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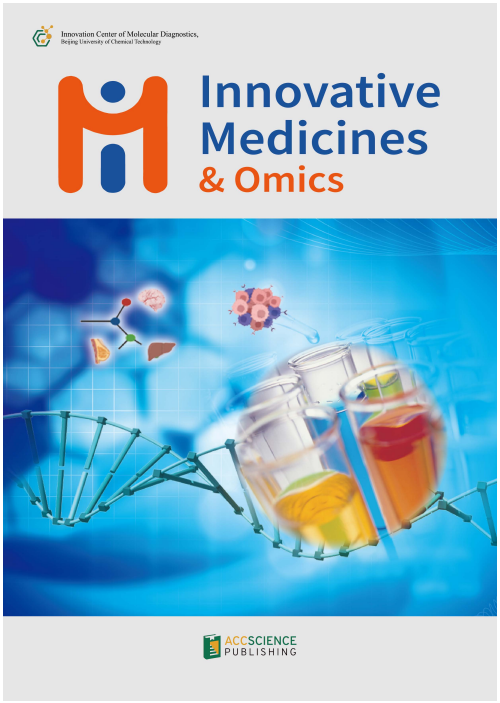

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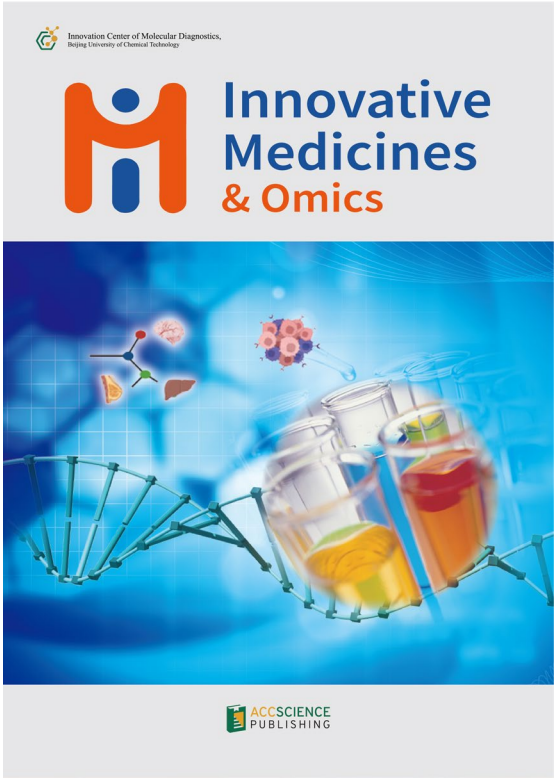

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REVIEW ARTICLE

Obesity management: An update on the available pharmacotherapy

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Abstract

Obesity is a complex condition characterized by excessive fat accumulation, leading to significant health risks, including cardiovascular diseases, diabetes, and certain cancers. Its multifactorial etiology encompasses genetic predispositions, behavioral factors, like poor eating habits and sedentary lifestyles, and hormonal imbalances involving leptin and insulin resistance. In addition to lifestyle interventions, such as balanced diets and regular physical activity, pharmacological therapies play a pivotal role in managing obesity. Approved medications include orlistat, which inhibits fat absorption by blocking gastrointestinal lipases; liraglutide and semaglutide, which are glucagon-like peptide (GLP)-1 receptor agonists that regulate appetite and glucose metabolism; phentermine/topiramate, which combines appetite suppression and satiety enhancement; and naltrexone/bupropion, which modulates the brain's reward pathways to reduce food cravings. Advanced therapies, such as setmelanotide, target genetic deficiencies affecting appetite regulation, while tirzepatide, a dual gastric inhibitory polypeptide, and GLP-1 receptor agonist, enhances satiety and metabolic control. Bariatric surgery remains a viable option for severe cases. With the inception of individualized treatment plans and the ongoing research into genetic and metabolic factors, the development of targeted, effective therapies, devoid of serious adverse effects, continues to evolve, offering hope for improved obesity management.

Keywords: Obesity; Childhood obesity; Epidemiology of obesity; Causes of obesity; Clinical imaging of obesity; Anti-obesity medications; Weight management

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1. Introduction

Obesity is a disease in which excess body fat is accumulated to an extent that it may have an adverse effect on health. Known to be a chronic disease, it is a serious public health concern and influences the mental as well as physical state of a person.[1] In humans, it now seems to be normal practice that excess energy is applied as a fat deposit with further feed savings for important difficulty periods. Usually, physiological mechanisms control fat storage within a narrow range to maintain balance. Yet, in certain individuals, these mechanisms are perturbed, resulting in excessive fat accumulation and an imbalance of the body's energy regulatory systems.[2]

Body mass index (BMI) is a simple anthropometric measure that correlates height and weight (weight/height^2 [kg/m^2]), commonly used to identify whether there is excess

body fat and the extent of it, as well. The World Health Organization (WHO) defines overweight as having a BMI between 25 and 29.9 kg/m², and obesity as having a BMI ≥30 kg/m². BMI can be classified into three classes: Class I (BMI = 30 – 34.9 kg/m²), Class II (35 – 39.9 kg/m²), and Class III or obesity (≥40 kg/m²).[3] Apart from BMI, there are several alternative methods to measure obesity that can provide a more detailed understanding of a person's body composition. Waist-to-hip ratio measures fat distribution, with a higher ratio indicating a greater risk of metabolic conditions.[4] Waist-to-height ratio compares waist circumference to height, with a ratio above 0.5 suggesting an increased risk of health issues.[5] Body fat percentage estimates the proportion of fat versus lean mass and can be measured through methods like bioelectrical impedance or calipers.[6] Advanced techniques like dual-energy X-ray absorptiometry and hydrostatic weighing offer precise measurements of body fat and lean mass.[7] These alternatives can provide a more accurate picture of obesity, especially when BMI alone may not reflect true body fat or health risks.

Obesity increases a person's risk of having several medical disorders, including hypertension, dyslipidemia, Type 2 diabetes, cardiovascular disease, and certain types of malignancies, including esophageal, pancreatic, colon, and breast cancers.[8] Due to the multitude of associated health risks, obesity remains a complicated public health challenge that requires a multifaceted multidisciplinary approach.

2. Clinical imaging of obesity

As already mentioned, obesity is an intricate disease that can be explained as an abnormal fat deposition in the body. Different physical as well as metabolic complications can be produced. Individuals who are overweight usually display increased body girth, some signs of metabolic disturbance, and pathological changes to several bodily systems.[9]

Common clinical features that are linked to obesity include insulin resistance, dyslipidemia (high levels of cholesterol and triglycerides), hypertension, and hyperglycemia. Leptin and adiponectin, two important hormones in the metabolic process, are altered by obesity leading to multiple disorders like Type 2 diabetes, non-alcoholic fatty liver disease, and cardiovascular disorders. In fact, fat accumulation in the abdominal region is a major risk factor for cardiovascular disease and obstructive sleep apnea, a condition where breathing is halted for short periods during sleep.[10]

Childhood or adolescent obesity is commonly, though not exclusively, associated with comorbidities developed earlier in life, such as Type 2 diabetes and Type 2 diabetic hypertensive metabolic syndrome, which all in turn predispose individuals to the risk of diseases, potentially causing premature death or suffering. Obesity can also result in social stigma, loss of dignity, and perceived self-worth reduction, which contribute to the complexity of therapy.[11]

3. Causes of obesity

Obesity is a multifactorial disease that results from the interplay of genetic, biological, social, and environmental factors. For more than 30 years, research indicates that biopsychosocial factors often outweigh individual choices in the weight gain balance.[12]

Some examples of factors that intensify risk include the genetics impact on syndromic, monogenic, and polygenic obesity, especially in children with severe childhood obesity. Less well understood, but still involved in hunger and weight control, are other molecular pathways, though the hormonal regulation especially through the leptin-melanocortin pathway appears to be particularly prominent.[13]

The rise in obesity in recent decades can be attributed to a combination of environmental, behavioral, genetic, and societal factors. Modern diets are dominated by high-calorie, nutrient-poor processed foods, larger portion sizes, and frequent snacking, all of which contribute to excessive calorie consumption. Sedentary lifestyles have become prevalent due to increased screen time, reduced physical exercise, and reliance on cars, buses, and trains for transportation. Furthermore, the aggressive food marketing and the mushrooming of dessert options have made healthy diet choices less accessible. Stressful work patterns, economic constraints, and psychological factors such as stress and emotional eating also exacerbate the problem. Moreover, public health challenges, including a lack of awareness and inadequate policies, also hinder efforts to promote healthier lifestyles. Furthermore, socioeconomic status is relevant to obesity prevalence as poverty and obesity rates are often linked in rich nations. Thus, the relationship between obesity and poverty presents a much complex picture than it may seem when prevalence of the pathological condition is dissected from a socioeconomic perspective.[14]

The most common type of obesity in children and adolescents is characterized by an imbalance between intake and expenditure of calories, promoting, as already mentioned, the risk for comorbid conditions, such as Type 2 diabetes, hypertension, and non-alcoholic fatty liver disease. Emotional issues, such as stress and psychological disorders, may also be a cause for abnormal eating habits, particularly emotional eating. Dietary patterns are

obviously very well received within a family or community setting, while high economic pressures lead make most people to opt for cheaper high-calorie foods. In essence, obesity is caused by two major classes of factors: personal biology and the larger social factors.[15]

4. Childhood obesity and the impact of COVID-19: Sedentary lifestyle and other effects

Nowadays, obesity is recognized as a growing global public health crisis in children and adolescents, having affected millions of people. According to the WHO, more than 340 million children and adolescents aged 5 – 19 years are overweight or obese. It is an upward alarming trend with long-term psychological problems and increased health conditions. Obesity has effects of utmost relevance to physical and metabolic health and to the risk of non-communicable diseases, such as cardiovascular disease, Type 2 diabetes, hypertension, and sleep apnea syndrome. In addition, it is associated with insulin resistance and chronic inflammation. Childhood obesity also leads to a few psychosocial consequences like low self-esteem, depression, and social stigmatization. When taken all together, these disorders result in reduced quality of life in the affected children and adolescents.[16]

The COVID-19 pandemic has further increased the risks of obesity. Obese children share similar risk factors with adults: underlying cardio-respiratory disorders, compromised immune function, and chronic clinical inflammation. These are the reasons why they are more at risk of experiencing grave side effects of such infections as COVID-19. Children who are obese tend to have weaker immune systems, which render them vulnerable to bacterial pneumonia infection which is among the most common and severe complications associated with COVID-19.[17]

The pandemic has also exacerbated sedentary behaviors, with increased screen time, consumption of unhealthy foods, and sleep disturbances contributing to increased weight gain and accumulation of central fat. Disruptions in daily routines, including stress from illness and increased time indoors, have impeded children's ability to maintain healthy sleep patterns. Moreover, a number of genetic and environmental factors have also been associated with obesity in childhood. These include habits of behavior, sociocultural and socioeconomic influences leading to poor eating habits, sedentary life, and lack of sleep. Prevention programs should be designed focusing on practical, effective solutions to ensure optimal, long-term health for all children and help to reduce health inequities.[18]

5. Epidemiology of obesity

Obesity has become a major worldwide health problem since gaining official public health epidemic status by the WHO in 1997. Obesity has more than tripled in prevalence globally over the past 40 years.[19] Today, about one-third of the world population is affected; there are 609 million adults, or 39% of the world's population who are obese, and more than 1.9 billion people are overweight.[20]

While this upsurge is more pronounced in females and older individuals, such a trend can be seen in all age groups, both sexes and in all countries. Obesity is now as common and widespread as undernutrition. At least 2.5 million adults die each year worldwide as a result of being overweight or obese. Overweight and obesity are rapidly gaining momentum, becoming one of the most serious public health challenges of the 21st century. Children today, either in the Western population or worldwide, may face a shorter life span due to obesity.[21,22]

Obesity is rising in all countries (not only those with a high income). The prevalence of obesity is climbing in low- and middle-income countries, especially in urban areas. For instance, in China, the rate of obesity has increased from 2.15% to 13.99% within just 22 years.[23] Childhood obesity has been a major concern too, with the share of overweight children aged 5 – 19 years old rising from 10% in 2000 to 18% by 2018. Furthermore, around 41 million children under five were overweight in the world in 2019.[24]

Obesity is now referred to as a term sociologists call a global synergistic epidemic alongside undernutrition and climate change. In fact, studies suggest that if the current trend continues, the figures for obesity will reach their highest level between 2030 and 2052. If this trend persists, the US and the UK will see an incidence of obesity of 44% in males and 37% in females. On the opposite extreme, obesity incidence is highest in Denmark and the Netherlands. This emerging trend poses great risks to economies and health systems across the globe.[25]

6. Health impacts of obesity: Associated diseases and risks

Obese states put one in a health risk, as 5 million deaths annually arise due to non-communicable diseases such as heart disease, diabetes, cancer, and respiratory diseases. Childhood and adolescent obesity enhances the risks for chronic diseases in adulthood and also diminishes social life, mental health, and quality of life due to stigmatization and prejudices faced. Obese children are most likely to be obese in their adulthood. It is also alarming in terms of economic burden, as it is predicted that the cost of obesity

will reach $3 trillion annually by 2030 and $18 trillion by 2060. In addition, it is not merely a problem of high-income nations because the rates of obesity are also escalating in nations with low and middle incomes, making it a global health challenge.[26]

At the biological level, obesity is characterized by low-degree systemic chronic inflammation backed by adipose tissue. Acute-phase proteins like C-reactive protein are raised due to important inflammatory markers such as interleukin (IL)-1, IL-6, IL-8, and tumor necrosis factor alpha. Thus, an inflammatory milieu is established, with both known and supposed ramifications.[27] Long-term cardiovascular complications of obesity include an increased risk of atherosclerosis and heart disease, particularly when the condition begins in young adulthood. The condition is associated with an increased mortality rate and tends to be chronic over time – these risks are improved by weight loss.[28]

Furthermore, obesity depletes homeostasis, increasing blood pressure, giving rise to kidney damage, fostering endothelial dysfunction, oxidative stress, and liver diseases such as steatosis, increasing blood volume, and modifying heart geometry.[29]

7. Obesity as a public health issue: Socioeconomic consequences

Healthcare expenditure may increase as a result of obesity's comorbidities, such as asthma, sleep apnea, diabetes, and liver disease, due to their long-term treatment and increased demand for medical services. Indeed, with the rising trend in diseases related to obesity, especially in children, it portends a generation living shorter lives compared to their parents, emphasizing long-term public health implications.[30]

It also hides a cost burden on the employers' side. As the rate of obesity within the labor force is increasing, the productivity losses arising due to health problems or absenteeism, or loss of efficiency at workplace add to an economic cost burden. The employers therefore should realize the consequence of obesity on work performance and offer the option of weight loss programs or health intervention at the workplace that could offset some of the economic costs.[31]

Income is a factor socially governing the rate of obesity. It is expected that the richer someone is, the more value-added nutrients he has access to and the wider opportunity he has for physical activities, which gives him/her added insurance for good health. Economic constraints on practicing healthy eating and active lifestyle plague members of lower-income groups more frequently, hence leading to higher rates of obesity. This reflects the socioeconomic gradient in health whereby the poorest are at risk of suffering from obesity-related diseases.[32]

While the dietary policy and environmental changes have been very effective in preventing obesity within the childhood population, combining these approaches with education is lacking in most programs. Indeed, without systemic comprehensive changes, simple educational efforts are entirely too little to try to stem the growing tide of obesity.[33]

Once thought to be comparatively a minor health issue, obesity has grown to become a major worldwide priority in public health. Although the condition was first identified in 1948, it has long been perceived as a "personal lifestyle choice" that can be easily overcome with exercising through enhanced willpower. Observations from the last few decades have, however, shown that obesity is, in fact, a multifaceted disease itself rather than an etiological cause for a large number of diseases. This type of postulation has been gaining traction in the last ten years, especially when obesity began to morph from an invisible problem into one of medical significance for health systems around the world.[34]

During recent decades, obesity has turned into a serious health problem both in developed and developing countries. Since it puts a considerable burden on the healthcare system due to higher morbidity and mortality from chronic, debilitating states associated with it, the following should be accomplished. It affects every age group and all socioeconomic strata of population composition, but increasing rates of childhood obesity are of special concern since they pose long-term health risks.[35]

Obese cases are becoming increasingly prevalent throughout the world at every level of income. Although these vary by geographical region, sociodemographic, behavioral, and genetic factors, all have contributed to its rise. Various biomarkers such as oxidative stress, microRNA, and adipocytes have been unraveled for predicting and diagnosing obesity, but a thorough understanding of the condition is yet to be achieved.[36]

8. Expenditure on obesity: A comparison of costs in the United States and Europe

Due to the high prevalence, obesity represents a global public health issue entailing considerable economic consequences both in Europe and the US. At an average prevalence of 15.9%, US adults are affected by obesity at 36.5%, while those in Europe reach 15.9% accordingly. Regarding financial consequences, which are very

significant due to the pervasiveness of the problem, they pertain to the healthcare industry the most.[25]

Considering the extent of obesity, the medical care costs are increased by as much as 100% for obese adults compared to people of normal weight. For instance, as compared to normal-weight individuals, class three obesity cases have annual medical expenses increased by 233.6%. The estimated cost spent to address obesity-related medical expenses within the US was $260.6 billion dollars in 2016. Among individuals who have been covered under a public health insurance program, their obesity-related medical expenses were $2,868 more compared to those covered under private insurance. The cost of spending for healthcare continues to rise, involving prescription medication costs, inpatient and outpatient care.[37]

Obesity also has a comparable economic burden in the European continent; German studies cite that the costs due to obesity can amount to 0.61% of the gross domestic product. Depending on the level of obesity and the socioeconomic status of the subject, per capital direct costs were between €117 and €1,873. The higher the socioeconomic status, the more healthcare costs due to obesity are encountered among obese subjects, especially those with more extreme.[38] These figures indicate that targeted interventions are urgently needed, which could reduce the prevalence of obesity, stop the increasing trend, and decrease the economic burden related to it.[39]

9. Economic, social, and health benefits of reducing obesity

It is crucial to realize that reducing obesity will have profound implications for the individual, community, and greater society as a whole. Economically speaking, controlling obesity could reduce healthcare costs substantially. It is already known that obesity ranks as one of the leading causes of chronic diseases, such as heart disease, Type 2 diabetes, and certain types of cancer, which entail very costly healthcare expenses around the world. By reducing the prevalence of obesity, the incidence of those diseases will be lowered, which in turn reduce the medical treatments required, hospitalizations, and long-term care. Healthier individuals also tend to have fewer sick days and to be more productive at work, thus contributing favorably to the overall economy.[40]

Socially, the decrease in obesity could promote a better quality of life of individuals due to increased physical health, mental health as well as socializing. Stereotyped by social stigma, which hurts self-esteem, engagement in social activities is bound to decrease. Being able to address obesity may also give the individual confidence, reduced anxiety levels, and enhanced perception of one's place in society. They may be more involved in community affairs and bear a positive impact on social cohesion and social participation.[41]

From a health perspective, the benefits of reducing obesity are undeniable. The share of weight that one loses reduces the acute risk of chronic diseases such as hypertension, sleep apnea, and osteoarthritis. It also enhances mental health and reduces the symptoms of depression and anxiety. A longer life expectancy has long-term health advantages, better mobility, and quality of life. After all, the reduction of obesity has great individual health benefits and also extends to be a broad benefit to the general community through improved health, heightened productivity, and better social connectivity.[42]

10. Methods of treating obesity without medications

Obesity management can be improved in multiple ways. There should be a more systematic program of integrative lifestyle interventions, such as dietary modifications, physical activity, behavioral therapy, sleep and stress management, better education and training, and end-to-service utilization of advanced digital health technologies.[43]

10.1. Dietary modifications

Some approaches for managing obesity without using medications are dietary modifications. Caloric intake, for people with obesity, should be lowered to 800 – 1,200 kcal/day for those weighing <114 kg and 1,200 – 1,800 kcal/day for those weighing ≥114 kg.[44] Furthermore, the diet should contain balanced portions of carbohydrates, fruits, vegetables, legumes, and whole grains, with saturated fats replaced with polyunsaturated fatty acids to reduce obesity. Very low-calorie diets permit better short-term weight loss, but long-term outcomes are usually disappointing due to metabolic adaptation and challenges of maintaining the diet. A sustainable caloric deficit and long-term change in eating patterns show the greatest promise regarding longevity in weight control.[45]

10.2. Physical activity

The patients should engage themselves with aerobic exercises, such as walking, cycling, and swimming to achieve weight loss, for at least 225 – 420 min/week, and maintaining weight loss for 200 – 300 min/week. Correspondingly, added with warm-up and cool-down exercises, aerobic and resistance training will enhance cardiorespiratory fitness and make this overall management of weight possible.[46]

10.3. Psychological approach

Cognitive-behavioral treatment of obesity is a tailored treatment that links conventional behavioral treatment

to cognitive methods in an effort to address factors of influence in weight loss and long-term maintenance. This approach includes self-monitoring, goal setting, problem-solving, and preventing relapse – specifically adapted to the needs of the patient. Weight loss effect of this approach is considerable, evidenced by patients reporting achievement of as much as 15% body weight reduction after 12 months, suggesting that this therapy may prove to be more effective than traditional weight-loss programs.[47]

10.4. Lifestyle modifications

Both sleep and stress are significant contributors to the reduction in obesity. For instance, poor sleep duration such as 5.5 h is associated with less fat loss and higher losses of muscle mass compared to sufficient sleep, which is usually considered to be 8.5 h of sleep, besides having higher levels of hunger and changes in the way fat is metabolized in the body. Sleep deficiency keeps the human body fueled with hunger, hence probably leading to overeating and interference with losing weight.[48] Furthermore, emotional stress linked to sleep disturbance may exacerbate obesity, and thus underscore the need for major management in the treatment of obesity.[49]

10.5. Support groups and counseling

Support systems for obesity can be strengthened by adopting global strategies, interdisciplinary collaboration, and systems such as mapping and modeling. Furthermore, the adoption of both traditional approaches and new methods, while bridging gaps of research and education with policy and action, should improve the prevention and control of obesity.[49] Moreover, the establishment of support groups that include patients, dietitians, personal trainers, and psychologists helps patients stay more consistent and dedicated to their weight loss endeavor.

10.6. Bariatric surgery

Bariatric surgery is a choice for those obese patients, where other treatments have failed, generally in people with a BMI above 40 or those with a BMI above 35 with comorbid conditions. There are many different surgical techniques, spanning from laparoscopic to open procedures, all of which lead to greater weight loss compared to conservative management and improvement in obesity-related comorbid conditions.[50] Surgery is indicated for the patient to attain major weight loss, but it does require sensitive counseling and also well-oriented medical team participation, including psychologists, dietetics, and specialized healthcare professionals. The patients should be informed about the potential complications and realistic expectations of success.[51]

11. Pharmacotherapy of obesity

The criteria for an obese patient to start medication include low motivation and commitment, uncontrolled BMI, and failed lifestyle modifications.[52] The early treatment along with progressive behavior modification is one of the most important steps. An obese individual may consider starting medication when their BMI is 27 or higher with at least one comorbidity, or when their BMI is 30 or above.[49] Medical treatments combined with behavioral and psychological interventions may achieve appropriate weight loss and enhancement of long-term success despite previous difficulties in weight management.[53] Table 1 reviews the approved medications for obesity management, recommended dosage, mechanism of action, possible side effects, and contraindications, whereas Figure 1 shows the timeline of the Food and Drug Administration (FDA) approval of these drugs.

11.1. Orlistat

Orlistat is the saturated derivative of lipstatin, a potent natural inhibitor of pancreatic lipases isolated from the bacterium *Streptomyces toxytricini*. However, due to its relative simplicity and stability, orlistat was chosen over lipstatin for development as an anti-obesity drug. Orlistat prevents fat from being absorbed, hence decreasing the overall caloric intake. It has been documented to cause significant reduction of body weight, visceral fat, and its related disorders such as hypercholesterolemia, insulin resistance, and blood glucose levels in clinical tests. Recent studies have also considered its use in cancer treatment. Orlistat, in fact, has emerged to inhibit tumor growth through interference with key cellular pathways, induction of tumor cell death, and interference with the growth cycle. The involvement of orlistat in obesity and cancer underlines its other important therapeutic role beyond weight management.[54] As an inhibitor of gastrointestinal lipase, orlistat plays an important role by inhibiting enzymes in lipid metabolism, preventing triacylglycerol from undergoing hydrolysis to fatty acids and nitro-

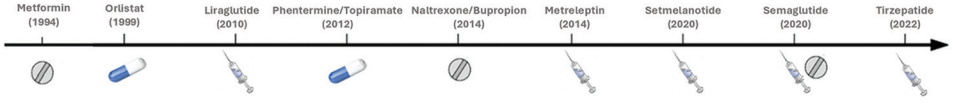

Figure 1. Timeline of FDA approval for obesity management drugs
Abbreviation: FDA: Food and Drug Administration.

Table 1. Summary of drug medications for obesity management

Drug (trade name)/Form	Dose	Mechanism of action	Adverse effects	Contraindications	FDA approval
Orlistat (Xenical®)/Capsules	120 mg 3 times daily	Inhibits pancreatic and gastric lipases, enzymes responsible for breaking down dietary fats. This prevents~30% of consumed fat from being absorbed, reducing calorie intake.	Abdominal pain or discomfort, oily stools, flatulence, diarrhea, frequent bowel movements, urgency to defecate	Chronic malabsorption syndrome, severe liver dysfunction, pregnancy, breastfeeding	1999
Liraglutide (Saxenda® for weight loss and Victoza® for Type 2 diabetes)/SC injection	Starting dose: 0.6 mg daily for 1 week Titration: increase dose by 0.6 mg weekly until the maintenance dose of 3.0 mg daily Max dose: 3.0 mg daily	GLP-1 receptor agonist that increases insulin secretion, reduces glucagon release, slows gastric emptying and reduces appetite, helping to control blood glucose and promoting weight loss.	Gastrointestinal issues, hypoglycemia, headache, fatigue, injection side reactions	Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia Type 2 , history of pancreatitis or pancreatic disease, severe gastrointestinal disease, pregnancy, breastfeeding	2010 for the treatment of Type 2 diabetes (Victoza) 2014 for chronic weight loss (Saxenda)
Phentermine/Topiramate (Qsymia®)/Capsules	Starting dose: 3.75 mg/23 mg Max dose: 15 mg/92 mg once daily	Phentermine suppresses appetite by stimulating norepinephrine release. Topiramate reduces appetite and enhances satiety through neurotransmitter modulation.	Paresthesia, dry mouth, constipation, insomnia, dizziness, altered taste	Pregnancy, glaucoma, hyperthyroidism, history of cardiovascular disease, severe renal impairment, MAOI use, hypersensitivity	2012
Naltrexone/Bupropion (Contrave®)/Tablets (each tablet contains 8 mg of naltrexone and 90 mg of bupropion)	32 mg/360 mg daily; 2 tablets taken twice daily.	Naltrexone: an opioid antagonist that reduces appetite by modulating the brain's reward system. Bupropion: a dopamine and norepinephrine reuptake inhibitor that enhances energy expenditure and reduces food cravings.	Gastrointestinal issues, headache, insomnia, dizziness, dry mouth	Seizure disorders, current or past eating disorders, opioid use, uncontrolled hypertension, MAOI use, hypersensitivity, pregnancy, breastfeeding	2014
Metreleptin (Myalept®)/SC injection	Starting dose: 0.06 mg/kg/day Max dose: 0.13 mg/kg/day	Mimics leptin, regulating appetite, energy balance, and fat metabolism, improving weight management in leptin-deficient conditions.	Headache, nausea, fatigue, hypoglycemia, liver enzyme elevation, immune system responses	Pregnancy, breastfeeding, active or recent infection	2014
Setmelanotide (Imcivree®)/ SC injection	1 mg once daily Max dose: 2 mg once daily	Activates melanocortin-4 receptors, enhancing appetite regulation and energy balance, specifically targeting obesity caused by genetic defects.	Headache, nausea, fatigue, irritability, diarrhea, and elevated liver enzymes	Liver impairment, kidney impairment, pregnancy and breastfeeding	2020

(Cont'd...)

Table 1. ***(Continued)***

Drug (trade name)/Form	Dose	Mechanism of action	Adverse effects	Contraindications	FDA approval
Semaglutide (Wegovy® for weight loss and Ozempic® for type 2 diabetes)/SC injection (Rebelsus®) tablets	Starting dose: 0.25 mg once weekly Max dose: 2.4 mg once weekly Rebelsus dosage starts at 3 mg daily, increasing to 7 mg or 14 mg	Mimics GLP-1, increasing insulin secretion, reducing glucagon, slowing gastric emptying, and reducing appetite to promote weight loss.	Nausea, vomiting, diarrhea, constipation, abdominal pain, lesser appetite	Personal/family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2, history of pancreatitis, pregnancy, breastfeeding, diabetic retinopathy.	2021
Tirzepatide (Mounjaro®)/ SC injection	Starting dose: 2.5 mg Titration: increase dose by 2.5 mg weekly until the maintenance dose of 12.5 mg daily Max dose: 15.0 mg	Activates both GIP and GLP-1 receptors, enhancing insulin secretion, reducing glucagon release, and improving glucose control and satiety.	Nausea, vomiting, diarrhea, decreased appetite, constipation, abdominal pain, and injection site reactions; serious effects may include pancreatitis, gallbladder issues, and kidney problems	Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2, pregnancy and breastfeeding, severe gastrointestinal disease	2022
Metformin (Glucophage Immediate release-IR®, Glucophage Sustained release-SR®/Tablets, Glucophage Extended Release-ER®/Tablets)	*Immediate-Release (IR) Tablets* Adults: 500 mg twice daily or 850 mg once daily with meals Titration: Increase by 500 mg weekly or 850 mg every two weeks based on tolerance Max dose: 2,550 mg/day (divided into 2 – 3 doses) Extended-Release (ER) Tablets Adults: 500 mg or 1,000 mg daily with dinner. Titration: Increase by 500 mg weekly. Max dose: 2,000 mg/day Sustained-Release (SR) Tablets Adults: 500 mg once daily with dinner Titration: Increase by 500 mg weekly based on tolerance Max Dose: 2,000 mg/day (some guidelines allow up to 2,500 mg in divided doses) For children: Metformin SR/ER starting dose: 500 mg once daily with dinner Titration: Increase by 500 mg weekly based on tolerance Max dose: 2,000 mg/day (in one or two doses) Immediate-release (IR) starting dose: 500 mg twice daily Max dose: 2,000 mg/day (divided into 2 – 3 doses)	(1) It modulates the hypothalamus, the brain's appetite control center, leading to reduced hunger and lower food intake. (2) Increases insulin sensitivity, metformin helps lower insulin levels, which prevents fat storage and supports fat breakdown. (3) Reduces hepatic glucose production, which helps in better glucose regulation and reduces fat accumulation. (4) Alters gut microbiome, promoting beneficial bacteria that influence metabolism and weight regulation. (5) Slows gastric emptying, leading to prolonged satiety, which helps reduce overall calorie consumption.	1. Gastrointestinal (most common): nausea, diarrhea, abdominal pain, bloating, loss of appetite, flatulence (gas) 2. Vitamin deficiency: Vitamin B12 deficiency (with long-term use), causing fatigue, numbness/tingling, memory issues 3. Lactic acidosis (rare but serious): Symptoms: weakness, dizziness, difficulty breathing, irregular heartbeat, severe fatigue, confusion 4. Hypoglycemia (low blood sugar): Rare, only occurs if combined with insulin or other diabetes medications. 5. Metallic taste in mouth: Some people report a metallic or bitter taste, which usually fades over time.	In severe kidney disease (eGFR<30 mL/ min/1.73 m^2), acute or unstable conditions that can cause lactic acidosis, metabolic acidosis (including diabetic ketoacidosis), contrast dye procedures (e.g., CT scan with IV contrast), alcohol abuse (chronic heavy drinking), pregnancy and breastfeeding (use with caution)	1994

Abbreviations: CT: Computed tomography; eGFR: Estimated glomerular filtration rate; GLP: Glucagon-like peptide; IV: Intravenous; MAOI: Monoamine oxidase inhibitor; SC: Subcutaneous; FDA: Food and Drug Administration, GIP: Gastric inhibitory polypeptide.

glyceride that are absorbed. Orlistat can also remove triacylglycerol from the body directly, with consequently reduced caloric intake or weight control.[55]

In adults, the recommended dose of orlistat is one 120 mg capsule with each main meal. The capsules may be taken immediately before, during, or up to 1 h after the meal. The patient should be on a well-balanced, mildly hypocaloric diet that contains approximately 30% of calories from fat. The daily intake of fat, carbohydrate, and protein should be distributed as evenly as possible over three main meals.[56]

Gastrointestinal adverse effects associated with orlistat, include oily stools, diarrhea, abdominal discomfort, and fecal incontinence. Symptoms are usually mild-to-moderate. There have been rare post-marketing reports of severe hepatic adverse events with orlistat, including cholestasis and liver failure. While orlistat seems to have positive effects regarding non-alcoholic fatty liver disease, the benefits it elicits through weight loss exert a favorable effect on blood pressure. Some of the studies found that orlistat has no effect on calcium, magnesium, and iron balance, with no effects on bone health markers either. Nevertheless, orlistat administration can be associated with acute kidney injury in exceptional cases due to fat malabsorption promoting enhanced oxalate absorption that subsequently leads to kidney stones. On the other hand, the agent is known for its carbohydrate metabolism improvement. Importantly, orlistat is also associated with interfering with a number of other drugs absorption. Furthermore, orlistat utilization would suppress the bioavailability of fat-soluble vitamins, necessitating supplementation in consumers to address this issue.[57]

Orlistat should not be used in the presence of chronic malabsorption syndrome, cholestasis, pregnancy, and breastfeeding, or in patients with a previous history of calcium-oxalate stones.[58]

11.2. Liraglutide

Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist, which is also known as incretin mimetics. It works by increasing insulin release from the pancreas and decreases excessive glucagon release. Moreover, liraglutide reduces food intake and causes weight loss through actions on both peripheral and central pathways by stimulating the hindbrain and hypothalamus. Consequently, appetite decreases and metabolism improves. Liraglutide has also been shown to sustain weight loss and concurrently provides cardiovascular benefits through the reduction of systolic blood pressure and improvement in glycemic control.[59]

Liraglutide is administered once a day and subcutaneously in the thigh, upper arm, or abdomen. It is initiated with a low dose (0.6 mg/day) for the first week. Then the dose is increased weekly to 1.2, 1.8, 2.4 mg/day, and up to 3 mg/day. If there is intolerance, dose titration may be slower, and maximum tolerated dose may be continued if weight loss is maintained.[60]

Gastrointestinal side effects such as nausea and/or vomiting are common with liraglutide. Weight-reducing effect is partially due to suppression of appetite. These side effects may be transient, and diminish over time. Diarrhea, anorexia, and low blood sugar also may be observed. Less common side effects are renal impairment, gallbladder disease, or pancreatitis.[61]

Pregnancy, breastfeeding, personal or family history of multiple endocrine neoplasia (MEN) 2A or 2B or medullary thyroid cancer, or previous hypersensitivity to liraglutide are contraindications to liraglutide use. To avoid hypoglycemia in patients using insulin secretagogue or insulin, dose reduction in these drugs may be necessary if liraglutide is added to the treatment.[62]

11.3. Topiramate-phentermine

Topiramate's (2,3:4,5-bis-*O*-(1-methylethylidene)-β-*D*-fructopyranose sulfamate) multifaceted weight loss processes include blocking voltage-gated sodium and calcium channels, which are involved in appetite regulation and brain signaling. Enhancement of gamma-aminobutyric acid receptors, a neurotransmitter that mediates a soothing effect on the brain, results in a decrease in hunger and curbing of food cravings. Topiramate acts by blocking specific glutamate receptors, known to be involved in the excitatory activity of the brain, further helping to curb appetite. The drug further inhibits carbonic anhydrase, an enzyme that intervenes in fat storage; this might reduce the accumulation of adipose tissue. These combined effects on appetite control, fat metabolism, and neural activity contribute to its weight-reducing properties, which make it an effective option in patients with obesity, especially when combined with phentermine. On account of its wide action on the nervous system, topiramate has adverse effects including tingling, cognitive disturbances, and dizziness, thus prompting careful monitoring by health practitioners.[63]

Topiramate and phentermine (2-methyl-1-phenylpropan-2-amine) are combined in the licensed weight-loss medication Qsymia. The initial dose for Qsymia is as follows: 3.75 mg of extended-release topiramate and 15 mg of phentermine taken in the morning, once a day. If required, the dosage can be raised after 14 days (depending on tolerance): 7.5 mg of extended-release topiramate and 37.5 mg of phentermine taken in the morning, once a day. If the drug is well tolerated and additional weight loss is

required, the dosage can be raised to 11.25 mg of extended-release topiramate and 37.5 mg of phentermine taken once daily, in the morning. The highest approved dose for Qsymia is 15 mg of extended-release topiramate and 75 mg of phentermine taken once daily, in the morning.

Weight loss may be possible with the topiramate and phentermine for obesity combination; however, there may be adverse effects which vary across users to varying degrees. The following list includes topiramate/phentermine side effects that are common. Typical adverse effects include dry mouth, constipation, fatigue or drowsiness, memory or concentration problems, anxiety, despair, mood swings, or irritation, speech difficulties or confusion, elevated heart rate or palpitations, elevated blood pressure, suicidal thoughts or behavior, vision problems, and kidney stones.[64]

The use of the combination of topiramate and phentermine, for the treatment of obesity, has certain contraindications. Topiramate should not be used by individuals with a history of kidney stones, glaucoma, liver impairment, respiratory issues, and during pregnancy. On the contrary, people with cardiovascular diseases, hyperthyroidism, glaucoma, during pregnancy or breastfeeding, or with a history of substance abuse, should not use phentermine. In general, the combination of the two medicines should be avoided in pregnant women, severe cardiovascular conditions, glaucoma, or a history of kidney stones.[65]

11.4. Naltrexone/Bupropion

Bupropion is a norepinephrine-dopamine reuptake inhibitor that was initially approved for depression but has shown weight loss in several studies. The weight effects are variable; however, the systematic review indicates that bupropion generally causes weight loss rather than gain. On the other hand, naltrexone is an opioid antagonist that works by antagonizing central opioid receptors, thus reducing food intake due to the blockade of β-endorphin at the μ-opioid receptor. The result is a reduced intake of foods, which supports weight reduction. The combination of bupropion and naltrexone exerts a synergistic effect on weight loss. Bupropion increases pro-opiomelanocortin (POMC) firing, which is involved in appetite regulation; naltrexone prevents the autoinhibitory feedback produced by β-endorphin on the POMC neurons. The combination helps sustain weight loss and manage obesity more effectively than either of the drugs given individually. Although the exact mechanisms of actions are being studied, this drug combination has shown promise in achieving marked weight loss among obese subjects.[66] The purpose of naltrexone/bupropion medication is to aid in weight loss for adults who are overweight or obese. This combination medication should be taken twice daily with 32 mg of naltrexone and 360 mg of bupropion each time. It comes in the form of extended-release tablets, allowing for their dosage gradually increased over the course of several weeks. The medication is designed to influence the brain's reward system, which helps to reduce appetite and cravings, supporting weight loss goals.[67]

The combination of naltrexone and bupropion can trigger several side effects, such as nausea, constipation, headache, dizziness, dry mouth, and insomnia. Some people may suffer from anxiety, increased blood pressure, or elevated heart rate. In a few circumstances, it can lead to seizures, liver problems, or psychiatric symptoms like depression or suicidal thoughts.[68]

The contraindications of naltrexone-bupropion are multiple. For instance, people with a history of seizures, eating disorders (*e.g.*, anorexia or bulimia), or uncontrolled hypertension, should not take these medicines as bupropion can lower the seizure threshold and elevate blood pressure. Furthermore, they should not be used with a combination of alcohol or opioid, as naltrexone may precipitate withdrawal symptoms. Furthermore, it is contraindicated in patients taking monoamine oxidase inhibitors or within 14 days of discontinuing them, due to potential interactions.[69] Recently, in an attempt to bypass these and other limitations, 3D printing technology has been utilized to develop personalized bupropion tablets.[70,71]

11.5. Metreleptin

Metreleptin is considered an analog of leptin, a hormone that plays an important role in controlling several factors, including energy balance, fat storage, and hunger. By binding to the leptin receptors (LEPR) in the hypothalamus, it helps decrease appetite, increase energy expenditure, and encourage fat metabolism. In patients with leptin deficiency or resistance, like those who have certain types of lipodystrophy, metreleptin can aid in normal leptin function restoration, leading to improved metabolic parameters such as better glucose control, lipid metabolism, and body weight. It is especially useful in treating hormonal imbalances caused by leptin deficiency, which can result in severe obesity and related issues.

Metreleptin is administered as a subcutaneous injection. The typical starting dose for adults and pediatric patients with generalized lipodystrophy is 0.06 mg/kg once daily. For patients with partial lipodystrophy, the recommended starting dose is 0.03 mg/kg once daily. The dose may be adjusted based on clinical response, but it should not exceed 1.0 mg/kg per day.

Metreleptin may cause side effects, including injection site reactions, headache, and abdominal pain. More

serious risks include the development of antibodies against this medicine, which could reduce its effectiveness. Some people may experience hypoglycemia, particularly when combined with other diabetes medications. Furthermore, there are concerns about the potential for liver enzyme elevations and the possibility of lymphoma in rare cases, especially in patients with underlying conditions like lipodystrophy.

Metreleptin is contraindicated in individuals with a known hypersensitivity to the drug or its components. It should not be used in patients with endogenous leptin production, as it may not be effective or appropriate. Metreleptin is also contraindicated in patients with uncontrolled active infections, especially those with a history of lymphoma or other cancers, as it may increase the risk of malignancy. In addition, it should not be used during pregnancy unless the benefits outweigh the risks.[72]

11.6. Setmelanotide

Setmelanotide is an octapeptide that focuses on melanocortin receptors, and specifically in MC4R, MC3R, and MC1R, in the hypothalamus. This peptide boosts MC4R signaling, which plays an important role in controlling satiety and appetite and as a result, it decreases hyperphagia and contributes to weight loss. This medicine has been clinically proven to promote weight loss in individuals with deficiencies in POMC and LEPR with noteworthy outcomes. Furthermore, the drug's metabolism yields peptides and amino acids with approximately 39% excreted unaltered in the urine. Setmelanotide is indicated for chronic weight management (weight loss and weight maintenance for at least one year) in people six years and older with obesity due to three rare genetic conditions: POMC deficiency, proprotein subtilisin/kexin Type 1 (PCSK1) deficiency, and LEPR deficiency confirmed by genetic testing demonstrating variants in *POMC*, *PCSK1*, and *LEPR* genes, which are considered pathogenic (causing disease), likely pathogenic, or of uncertain significance.

Setmelanotide is administered as a subcutaneous injection. The typical starting dose is 1 mg once daily, which may be increased gradually based on clinical response and tolerability, up to a maximum of 2 mg daily. The exact dose may vary depending on individual patient needs and physician recommendations.

Hypersensitivity at the injection site, including blistering, burning, hives, and skin discoloration, constitutes one of the most frequent side effects observed with setmelanotide. Other undesirable effects comprise sexual dysfunction, skin hyperpigmentation, depression, and suicidal ideation. MC4R receptor stimulation on melanocytes leads to hyperpigmentation, which is reversible but may raise concerns about melanocytic tumors. Sexual dysfunction, such as persistent erection in males, results from MC4R activation affecting sexual brain processing. Obese patients treated with setmelanotide are also at an increased risk of suffering from depression. The administration of this medication to neonates and infants is contraindicated due to the presence of benzyl alcohol, which could trigger fatal reactions such as gasping syndrome.

Setmelanotide is contraindicated during pregnancy due to potential risks to the fetus, such as benzyl alcohol-induced gasping syndrome. Weight loss while pregnant is not recommended. Furthermore, this medicine is not recommended with breastfeeding, as it may be excreted in milk. Due to limited safety data, it is not suitable for children under 6 or elderly patients over 65. Moreover, it is contraindicated in patients with moderate-to-severe renal impairment or end-stage renal disease, and not recommended for those with hepatic impairment.[73]

11.7. Semaglutide

Semaglutide is an antidiabetic medication used for the treatment of Type 2 diabetes and an anti-obesity medication used for long-term weight management. It is a peptide similar to the GLP-1 hormone, with a modification to its side chain. It is available as both a subcutaneous injection and an oral medication, with doses given as 0.25 mg, 0.5 mg, and 1 mg through subcutaneous injection once weekly, and 3 mg, 7 mg, and 14 mg orally once daily. The FDA has also approved semaglutide in June 2021 for the long-term management of weight using higher subcutaneous doses of 1.7 and 2.4 mg once weekly. Specifically, clinical trials on the semaglutide treatment effect in people with obesity have documented that semaglutide is effective for obesity management.[74]

The dose of semaglutide for obesity is usually initiated at a low dose and titrated upward to minimize adverse effects. The exact dosing and titration schedule depend on the formulation used (*e.g.*, Ozempic and Wegovy) and the patient's response to treatment. The general dosing schedule, which is specifically approved for weight management, is 0.25 mg injection once a week from week 1 to 4, 0.5 mg injection once a week from week 5 to 8, 1 mg injection once a week from week 9 to 12, 1.7 mg injection once a week from week 13 to 16, and 2.4 mg injection once a week at week 17 and beyond (with the latter being the maintenance dose).[75]

11.7.1. Mechanism of action of liraglutide and semaglutide

GLP-1 is an incretin hormone produced by enteroendocrine L-cells and α-cells in both the pancreas and the central

nervous system. Its main function is to stimulate insulin secretion in response to increased blood glucose levels. Besides, GLP-1 stimulates the growth and replication of pancreatic β-cells and reduces their apoptosis. The mechanism of action of GLP-1 is through the binding of the peptide to its receptor, a G protein-coupled receptor that activates multiple important intracellular pathways. One pathway includes adenylate cyclase, resulting in an intracellular increase in levels of cyclic AMP. The intracellular increase in cyclic AMP activates protein kinase A, which enhances the exocytosis of insulin-containing vesicles from pancreatic β-cells, thus enhancing glucose-induced insulin secretion. GLP-1 also inhibits the release of glucagon from pancreatic α-cells, which decreases glucose production by the liver.

11.8. Tirzepatide

Tirzepatide is a gastric inhibitory polypeptide analog and GLP-1 receptor agonist. It works by activating the GLP-1 receptors in the brain's hypothalamus, which controls appetite. GLP-1 receptor agonists reduce hunger and cause the patient to eat less by activating these receptors. To reduce appetite and promote fullness, GLP-1 receptor agonists also attach to the GLP-1 receptors on specific brain neurons. It has been demonstrated that they cause the sensation of fullness by delaying the emptying of the stomach during the 1st h after eating. GLP-1 receptor agonist users report feeling less hungry and arousing, preferring fewer high-calorie foods, experiencing less food cravings, and having greater overall control over their eating patterns.[76]

Tirzepatide (Mounjaro) comes as a pre-filled pen for subcutaneous injection. After four weeks, the starting dose is increased to 5 mg from the initial 2.5 mg once each week. Depending on response and tolerance, doses may be increased to 7.5 mg, 10 mg, 12.5 mg, or 15 mg/week.

Headache, nausea, vomiting, diarrhea, constipation, and abdominal pain are typical Mounjaro's side effects. Fatigue, decreased appetite, and dizziness are possible additional adverse effects. Rarely, this medicine results in severe adverse effects such as kidney issues, gallbladder illness, and pancreatitis. Hypoglycemia, or low blood sugar, can also occur in patients using Mounjaro. Hypoglycemia can cause dizziness, perspiration, shakiness, and confusion. Furthermore, thyroid hormone levels may fluctuate as a result of Mounjaro. Last but not least, Mounjaro could alter cholesterol levels. While using this drug, patients' cholesterol levels should be routinely monitored.[77]

Patients with MEN 2 or personal or family history of medullary thyroid cancer should not use Mounjaro. It is also contraindicated in individuals with a history of pancreatitis or severe gastrointestinal issues, as well as during pregnancy and breastfeeding.

11.9. Metformin

Recent research indicates that the weight loss associated with metformin may result from its effects on hypothalamic appetite regulation, changes in the gut microbiome, and the reversal of aging-related effects. In addition, metformin is being investigated for its potential in treating obesity-related complications, including hepatic steatosis, obstructive sleep apnea, and osteoarthritis.[78]

Metformin is administered orally in three different release rates: immediate release-IR®, sustained release-SR®/tablets, and extended Release-ER®/tablets. For adults, the IR tablets are administered 500 mg twice daily or 850 mg once daily with meals, with an increase of 500 mg weekly or 850 mg every two weeks based on tolerance. The maximum dose is 2,550 mg/day (divided into 2 – 3 doses). The ER tablets for adults are administered in 500 mg or 1,000 mg daily with dinner, with a dosage increase by 500 mg weekly. The maximum dose is 2,000 mg/day. For adults, the SR tablets are given 500 mg once daily with dinner and then increased by 500 mg weekly based on tolerance, with a maximum dose of 2,000 mg/day (some guidelines allow up to 2,500 mg in divided doses).[79] On the other hand for children, metformin SR/ER starting dose is 500 mg once daily with dinner and then increase by 500 mg weekly based on tolerance with maximum dose being 2,000 mg/day (in one or two doses). The starting dose of IR metformin for children is 500 mg twice daily with the maximum dose of 2,000 mg/day (divided into 2 – 3 doses).

Metformin is generally well-tolerated, but it can cause some side effects, particularly in the digestive system. Common side effects include nausea, diarrhea, abdominal discomfort, and bloating, especially when starting treatment. Long-term use may lead to a vitamin B12 deficiency. In rare cases, metformin can cause lactic acidosis, a serious condition that leads to muscle pain, difficulty breathing, and confusion, especially in individuals with kidney or liver problems. It can also cause a metallic taste in the mouth. These side effects are usually manageable with dose adjustments or by taking metformin with food.[80]

Another research conducted a 6-month study on 154 consecutive outpatients with a BMI ≥27 kg/m², treating them with metformin up to 2,500 mg/day, while 45 untreated patients served as controls. Weight changes were monitored, and before starting treatment, insulin sensitivity was assessed using the homeostasis model assessment and Matsuda indices after a 75 g oral glucose tolerance test. Results showed that the metformin group lost an average

of 5.8 ± 7.0 kg (5.6 ± 6.5%), whereas controls gained 0.8 ± 3.5 kg (0.8 ± 3.7%). Notably, patients with severe insulin resistance experienced greater weight loss, while age, sex, and BMI did not influence weight reduction.[81]

12. Weight loss supplements

12.1. *L*-carnitine

L-carnitine is a vitamin-like and an amino acid-like substance, which is synthesized in the liver and kidneys, using Vitamin C, iron, and niacin as precursors in its synthesis. The dietary sources where *L*-carnitine is abundant are meat, fish, and other animal-based products such as milk. It is essential for the oxidation of fatty acids in both skeletal and cardiac muscles since it facilitates the transportation of long-chain fatty acids into the mitochondria. Furthermore, *L*-carnitine is also implicated in the generation of reactive oxygen species, energy production, trapping of acetyl groups, and glucose metabolism. Most of these processes are believed to help in weight management. It is suggested that *L*-carnitine contributes to the management of obesity through its effects on blood glucose regulation and its lipid-lowering properties.[82]

12.2. Conjugated linoleic acid

Conjugated linoleic acid is a natural derivative of the omega-6 fatty acid linoleic acid. It usually occurs in dairy and meat products. In animal models, this supplement has been shown to have a variety of potential benefits, which include better management of diabetes, enhanced immune function, reduced biomarkers of atherosclerosis, and positive changes in body composition such as a reduction in body fat and an increase in lean muscle mass. Conjugated linoleic acid supplementation in humans has shown possible improvements in insulin sensitivity and lipid metabolism, characterized by the lowering of plasma triglycerides and reduction of low-density lipoprotein (LDL) cholesterol. Such changes imply an advantage in weight management and total metabolic health.[83]

12.3. Ginseng

Ginseng is the root of plants in the genus *Panax*, such as Korean ginseng (*Panax ginseng*), South China ginseng (*Panax notoginseng*), and American ginseng (*Panax quinquefolius*), characterized by the presence of ginsenosides and gintonin. Ginseng is common in the cuisines and medicines of China and Korea. Ginseng has been used in traditional medicine over centuries, though modern clinical research is inconclusive about its medical effectiveness.

The role of ginseng in weight management is an up-and-coming intervention by way of the modulation of appetite-regulating neuropeptides. A reduction in energy stores, common with weight loss, activates neuropeptides responsible for increased hunger, often resulting in failure. Ginseng and its active compounds, especially ginsenosides, act against this by suppressing orexigenic neuropeptides like neuropeptide Y and agouti-related peptide that stimulate appetite while enhancing anorexigenic neuropeptides such as cholecystokinin and POMC that reduce food intake. The network pharmacology analysis also suggests that compounds from ginseng, such as ginsenoside Rb1, campesterol, and biotin, link genes related to energy balance and food intake, therefore suggesting that ginseng might act as a natural adjuvant in weight management.[84]

12.4. Glucomannan

Glucomannan is a water-soluble fiber with high molecular weight and viscosity, which is very effective for weight loss. Glucomannan acts by absorbing water in the stomach and expanding, consequently creating a feeling of fullness and reducing overall food intake. In addition, glucomannan delays gastric emptying, which prolongs satiety and consequently decreases food intake. It has several benefits: the reduction of post-meal blood sugar spikes, reduction of cholesterol synthesis in the liver, and increased excretion of cholesterol through bile acids. Such mechanisms help in weight reduction, improved cholesterol levels, and better blood glucose control – all useful for glucomannan to be considered a helpful aid in weight management.[85]

12.5. Herbal medicines (green tea, hibiscus, cinnamon, and ephedra)

The extract of green tea has been documented to decrease weight, waist circumference, total cholesterol, and LDL levels in women with central obesity. On the other hand, *Hibiscus sabdariffa* extract helps reduce abdominal fat, serum-free fatty acids, and improves liver steatosis in obese individuals. Cinnamon consumption also caused a significant improvement in metabolic syndrome components in Asian Indians. *Ephedra sinica* has traditionally been used in China to reduce body weight, body mass, and fat percentage in obese women. Most herbal medicines act by promoting the reduction of body weight, usually through appetite suppression, enhancement of metabolic rate, lipolysis, and inhibition of fat accumulation, as induced by Ephedra, a classic sympathomimetic medication used as an appetite suppressant.[86]

12.6. Psyllium

Psyllium is a natural fiber, largely soluble, which forms a thick gel when it absorbs water and is neither digested nor fermented. In the small intestine, this gel increases the viscosity of the chyme, which slows the breakdown

and absorption of nutrients. Psyllium has been shown to improve glycemic control in patients with metabolic syndrome and Type 2 diabetes, as well as reduce cholesterol levels in patients with hypercholesterolemia. Several trials have also shown that psyllium can help reduce body weight in overweight or obese individuals.[87]

12.7. Melatonin

The pineal hormone melatonin (*N*-acetyl-5-methoxytryptamine) is characterized by multiple actions in the regulation of the circadian rhythm and weight control.[88] It acts on insulin synthesis and sensitivity, which is important for the maintenance of normal glucose levels. Melatonin promotes metabolic function through the regulation of GLUT4 expression and the activation of insulin signaling pathways. Besides, melatonin takes part in energy balance through the stimulation of brown adipose tissue and browning of white adipose tissue, enhancing energy expenditure. Disruptions in the production of melatonin with aging and/or environmental factors may affect insulin resistance, glucose intolerance, and obesity.[89]

Recent studies have shown that melatonin is useful for weight loss and for reducing fat mass. Animal studies showed that melatonin decreases weight gain and enhances fat loss, whereas some clinical trials in humans reported a reduction in body weight and BMI. Although a 2017 meta-analysis revealed no significant effect on body weight, some recent clinical trials have suggested that melatonin may be a useful dietary supplement for weight management. In light of such positive results, further meta-analyses are warranted to establish a more definitive role of melatonin in obesity management. In an attempt to personalize the dose of melatonin, based on patients' needs, scientists also applied 3D printing technology for the preparation of tablets and oral films.[90-92]

12.8. Cannabidiol

Many researchers have shown that cannabis-based remedies can treat a range of metabolic syndrome components such as obesity, high blood pressure, impaired glucose metabolism, and non-alcoholic fatty liver disease, with cannabidiol (CBD; 2-[(1*R*,6*R*)-6-Isopropenyl-3-methylcyclohex-2-en-1-yl]-5-pentylbenzene-1,3-diol) being of particular interest. More specifically, CBD may help sensitize adipose tissue to insulin and decrease fasting glucose levels, although results have been inconsistent. CBD also demonstrates potential in improving lipid profiles, lowering LDL, and increasing high-density lipoprotein. While CBD's hypotensive effects are moderate, it has been found to stabilize blood pressure and safeguard blood vessels. Its anti-inflammatory, antioxidant, and neuroprotective characteristics make it an appealing adjunct therapy for metabolic disorders, with data indicating that cannabis users tend to have lower BMI. However, additional research is necessary, especially concerning its effect on non-alcoholic fatty liver disease in humans. Therapeutic potential of CBD could help mitigate inflammation and comorbidities associated with obesity. Nonetheless, it will most likely be employed as a supplementary therapy rather than a primary treatment.[93,94]

13. Conclusion

Obesity is defined as a complex physical process in which fat accumulates in the body. Obesity causes critical health consequences, spanning from heart diseases to certain forms of cancer. As a multifactorial condition, its occurrence is more particularly attributed to genetic and behavioral factors. Behavioral factors mainly include poor eating habits. People who consume high-calorie/low-nutrient foods and who are living a sedentary lifestyle tend to become obese, and if compounded by a genetic predisposition and hormonal imbalances, particularly with regard to leptin and insulin resistance, their chances of fat accumulation will be increased.

Weight loss is achieved by lifestyle changes, such as a balanced diet and regular physical activity. Furthermore, pharmacological treatment provided by drugs, such as orlistat, liraglutide, phentermine/topiramate, naltrexone/bupropion, metreleptin, setmelanotide, semaglutide, and tirzepatide or supplements intake can support weight loss either by reducing fat absorption or by regulating appetite. In more severe cases of obesity, weight loss can be achieved by bariatric surgery as the last resort. Under most circumstances, the methods used to lose weight are subject to personal preferences. At present, ongoing research into genetic and metabolic factors in the context of obesity will continue to offer hope for the development of more targeted and effective treatments.

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ACCSCIENCE PUBLISHING

Innovative Medicines & Omics

REVIEW ARTICLE

Diabetes mellitus: An updated overview and role of medicinal plants in modern treatment

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Abstract

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by inadequate insulin production or peripheral insulin resistance, leading to persistent hyperglycemia. Prolonged hyperglycemia levels can cause severe complications, including nephropathy, neuropathy, retinopathy, and cardiovascular diseases. Diabetes is classified into four main types: Type 1 DM, type 2 DM, gestational DM, and maturity-onset diabetes of the young, each with distinct etiologies and clinical manifestations. Present therapeutic strategies encompass pharmacological interventions and lifestyle modifications; however, these approaches have limitations, such as adverse effects and reduced efficacy over time. Cutting-edge treatments, including stem cell therapy, gene therapy, nanotechnology, and medicinal plant-based therapies, offer promising avenues for improved diabetes management and potential cure. Several medicinal plants, including gudmar, bitter melon, and fenugreek, contain natural compounds that regulate blood glucose levels, boost insulin secretion, and mitigate oxidative stress, positioning them as valuable adjuncts in diabetes management. This review provides a comprehensive analysis of diabetes pathophysiology, classification, and present management strategies, highlighting the necessity for novel treatment approaches in response to the global diabetes epidemic.

Keywords: Diabetes mellitus; Pathophysiology; Treatment; Medicinal plants

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1. Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by insufficient insulin production and peripheral insulin resistance, leading to persistent hyperglycemia. Prolonged exposure to elevated blood glucose levels causes progressive damage to multiple organ systems,[1] primarily affecting adipose tissue, skeletal muscle, and the liver. These effects manifest at various physiological levels, including insulin receptors, signal transduction pathways, and/or effector enzymes or genes involved in glucose metabolism[2] (Figure 1).

The hallmark symptoms of hyperglycemia include polydipsia (increased thirst), polyuria (frequent urination), unexplained weight loss, blurred vision, and polyphagia (increased appetite). In addition, chronic hyperglycemia contributes to growth

abnormalities and an increased susceptibility to infections.[3] Over time, diabetes can lead to severe complications, such as diabetic nephropathy, neuropathy, retinopathy, obesity, and cardiovascular disease, resulting in progressive damage to the eyes, kidneys, heart, and nervous system.[1] Diabetes is currently classified according to its pathophysiological mechanisms and underlying etiology, which guide clinical assessment and treatment choice. The four main types of DM include type 1 DM (T1DM), type 2 DM (T2DM), gestational DM (GDM), and maturity-onset diabetes of the young (MODY).[4]

Globally, the burden of diabetes is escalating at an alarming rate. In 2021, approximately 537 million adults aged 20 – 79 years were diagnosed with diabetes, accounting for 10.5% of the world's population. This number is projected to rise to 643 million by 2030 and 783 million by 2045. In addition, 541 million individuals exhibited impaired glucose tolerance, placing them at heightened risk of developing diabetes. The rising trend of youth-onset T2DM is particularly concerning, as it leads to an earlier onset of complications and a prolonged lifetime disease burden. A major challenge in diabetes management is the high prevalence of undiagnosed cases, particularly in low- and middle-income countries, where nearly 240 million adults remain unaware of their condition. These statistics highlight the urgent need for improved diagnostic strategies and more effective therapeutic interventions.[5]

Present pharmacological treatments for diabetes, including metformin, sulfonylureas, insulin therapy, and newer agents such as sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, play a crucial role in glycemic control. However, these therapies are often associated with adverse effects, high costs, and limited long-term efficacy in disease prevention. Furthermore, accessibility remains a challenge, particularly in resource-limited settings.[6] Despite advancements in pharmacological therapies, there remains an increasing interest in medicinal plants as complementary or alternative treatments for diabetes.[7] Numerous plant-derived bioactive compounds have demonstrated antidiabetic effects through various mechanisms, such as enhancing insulin secretion, improving glucose uptake, and reducing oxidative stress.[8,9] Medicinal plants and their bioactive compounds offer a promising therapeutic approach, especially in regions with limited access to conventional treatments.

A recent review highlights the anti-hypoglycemic properties of several plants, such as *Allium sativum* (garlic), *Hibiscus sabdariffa*, and *Zingiber officinale* (ginger).[10] The study emphasized the role of these plants, along with vitamins, in managing diabetes by reducing blood glucose levels and inflammation. In addition, a systematic review of human clinical trials identified four prominent medicinal plants – *Curcuma longa* (turmeric), *A. sativum* (garlic), *Momordica charantia* (bitter melon), and *H. sabdariffa* (roselle) – that exhibited significant glucose-lowering effects.[11]

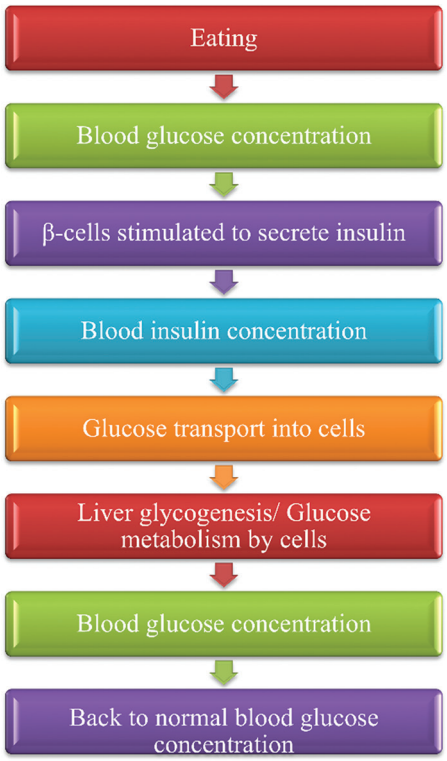

Figure 1. Overview of glucose metabolism, glycolysis, and the role of insulin

Given the growing scientific evidence supporting the role of medicinal plants in diabetes management, this review examines their therapeutic potential alongside conventional management strategies. It explores the pathophysiology, classification, and treatment strategies for DM, focusing on the therapeutic potential of medicinal plants as complementary or alternative treatments.

This review further explores the epidemiology of diabetes, emphasizing its increasing global prevalence and the urgent need for alternative therapeutic options. In addition, it discusses recent advances in conventional treatment strategies, the role of medicinal plants in glycemic control, and their potential to mitigate diabetes-related complications. The mechanisms by which medicinal plants exert antidiabetic effects, including their impact on insulin sensitivity, glucose metabolism, and pancreatic β-cell function, are also analyzed.

2. Epidemiology

The rising prevalence of diabetes is closely linked to lifestyle changes, obesity, and inadequate physical activity, all of which contribute to insulin resistance and metabolic dysfunction.[12] The increasing incidence of youth-onset T2DM presents long-term healthcare challenges.[13] These statistics underscore the urgent need for improved diabetes prevention, early diagnosis, and effective management strategies globally. According to the National Non-Communicable Disease Monitoring Survey, 9.3% of Indian adults aged 18 – 69 years have diabetes, while 24.5% exhibit impaired fasting glucose levels. However, the rates of awareness (45.8%), treatment (36.1%), and glycemic control (15.7%) remain suboptimal. Contributing factors include dietary shifts and insufficient physical activity, resulting in a higher prevalence of obesity, which further exacerbates the diabetes burden.[14]

3. Classification and pathophysiology of DM

Despite its complex causes and diverse clinical manifestations, the classification of DM remains crucial for accurate clinical evaluation and effective treatment selection. DM is primarily categorized into four primary types: T1DM, T2DM, GDM, and MODY.[15] The World Health Organization classification systems serve as a key reference, though emerging research highlights the necessity for updated classifications to better reflect the disease's heterogeneity.[16] Recent research has identified four distinct subtypes of DM, each associated with unique risk factors and treatment responses, highlighting the importance of precision medicine in diabetes management (Table 1).[17]

3.1. Type 1 DM

Type 1 DM is an autoimmune disease characterized by the destruction of insulin-producing pancreatic β-cells (Figure 2). The development of T1DM is influenced by genetic susceptibility and environmental triggers, which initiate an autoimmune response. Autoimmune markers, such as glutamic acid decarboxylase autoantibodies (GAD65), insulin autoantibodies (IAAs), and islet cell autoantibodies (ICAs), are commonly detected in T1DM patients.[18] The rate of β-cell destruction varies among patients. In children, the process is typically rapid, often leading to early-onset diabetic ketoacidosis, whereas in adults, β-cell destruction may occur more gradually, allowing for some residual insulin secretion during the early stages of the disease. Due to absolute insulin deficiency, T1DM necessitates lifelong insulin therapy.[22]

A range of autoantibodies is associated with T1DM, including tyrosine phosphatase autoantibodies (IA-2 and IA-2α), IAAs, ICAs, autoantibodies targeting islet cell antigen 512, GAD65, and autoantibodies against the islet-specific zinc transporter isoform 8.[23]

3.2. Type 2 DM

Type 2 DM is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from impaired insulin secretion and insulin resistance. T2DM accounts for over 90% of all diabetes cases globally.[24] The pathogenesis of T2DM involves progressive β-cell dysfunction, leading to inadequate insulin release, coupled with peripheral insulin resistance in skeletal muscle, liver, and adipose tissue.[25] Obesity, particularly increased visceral adiposity, plays a crucial role in disease progression by inducing low-grade chronic inflammation, excessive free fatty acid release, and adipokine dysregulation, all of which contribute to insulin

Table 1. Classification and pathophysiology of diabetes mellitus

Types of diabetes mellitus	Description	Percentage of case	Key characteristics	References
Type 1 diabetes mellitus	An autoimmune disorder characterized by the destruction of pancreatic β-cells that produce insulin.	5 – 10%	Autoimmune destruction, presence of autoantibodies (e.g., GADAs, ICAs, IAAs), typically juvenile-onset.	18
Type 2 diabetes mellitus	A metabolic disorder resulting from impaired insulin secretion due to β-cell dysfunction and insulin resistance in peripheral tissues.	90 – 95%	Insulin resistance and β-cell dysfunction, usually adult-onset, are associated with obesity and lifestyle factors.	19
Gestational diabetes mellitus	Usually happening in the 2nd or 3rd pregnancy trimester and resolving post-delivery.	1 – 14% of all pregnancies	Insulin resistance during pregnancy is a risk factor for future type 2 diabetes mellitus in both mother and child.	20
Maturity-onset diabetes of the young	A monogenic form of diabetes caused by mutations in a single gene affecting insulin secretion from β-cells upon glucose activation.	Smaller percentage	Impaired insulin secretion results from defects in pancreatic islet cell development.	21

Abbreviations: GADAs: Glutamic acid decarboxylase autoantibodies; IAAs: Insulin autoantibodies; ICAs: Islet cell antibodies.

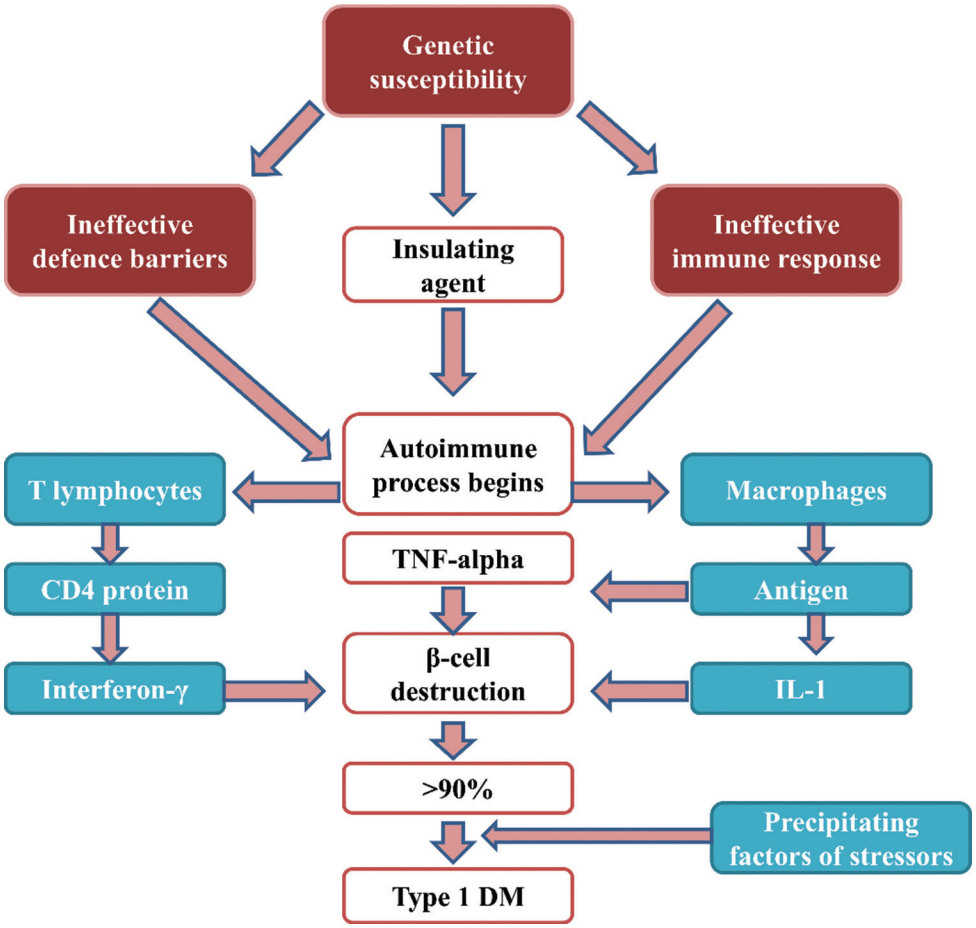

Figure 2. Pathophysiology of type 1 DM
Abbreviations: DM: Diabetes mellitus; IL-1: Interleukin-1; TNF-alpha: Tumor necrosis factor-alpha.

resistance.[19] As T2DM advances, defective insulin signaling exacerbates hepatic glucose overproduction and decreases glucose uptake in peripheral tissues, further aggravating hyperglycemia.[25] The global prevalence of T2DM has risen sharply, largely driven by sedentary lifestyles, high-calorie diets, and an aging population.[19] Effective T2DM management strategies focus on lifestyle interventions, pharmacotherapy, and emerging precision medicine approaches tailored to individual metabolic profiles (Figure 3).[24]

3.3. GDM

GDM is a transient form of diabetes characterized by β-cell dysfunction and increased insulin resistance, typically diagnosed during the second or third trimester. It frequently arises in women with pre-existing metabolic abnormalities, particularly in populations with a high prevalence of obesity and diabetes.[26] Pregnancy induces physiological metabolic changes that place additional stress on β-cells. During early pregnancy, normoglycemia is maintained through compensatory insulin secretion. However, as pregnancy progresses, insulin resistance increases, leading to hyperglycemia in susceptible individuals (Figure 4).[27] Women with GDM face a significantly increased risk of developing T2DM postpartum, primarily due to persistent β-cell dysfunction and sustained insulin resistance. Excessive gestational weight gain further exacerbates this risk.[28] In addition, only 2 – 13% of women diagnosed with GDM exhibit autoantibodies against β-cell antigens, suggesting that autoimmunity plays a minor role in its pathophysiology.[26] Effective management of GDM includes lifestyle modifications, regular glucose monitoring, and, in some cases, insulin therapy to reduce complications for both the mother and fetus.

3.4. Other specific types of diabetes

Monogenic diabetes, including MODY, results from single-gene mutations affecting β-cell function. While MODY comprises a small fraction of diabetes cases, its accurate diagnosis is essential for targeted treatment. This form of diabetes is typically inherited in an autosomal dominant manner and is characterized by early onset (often before the

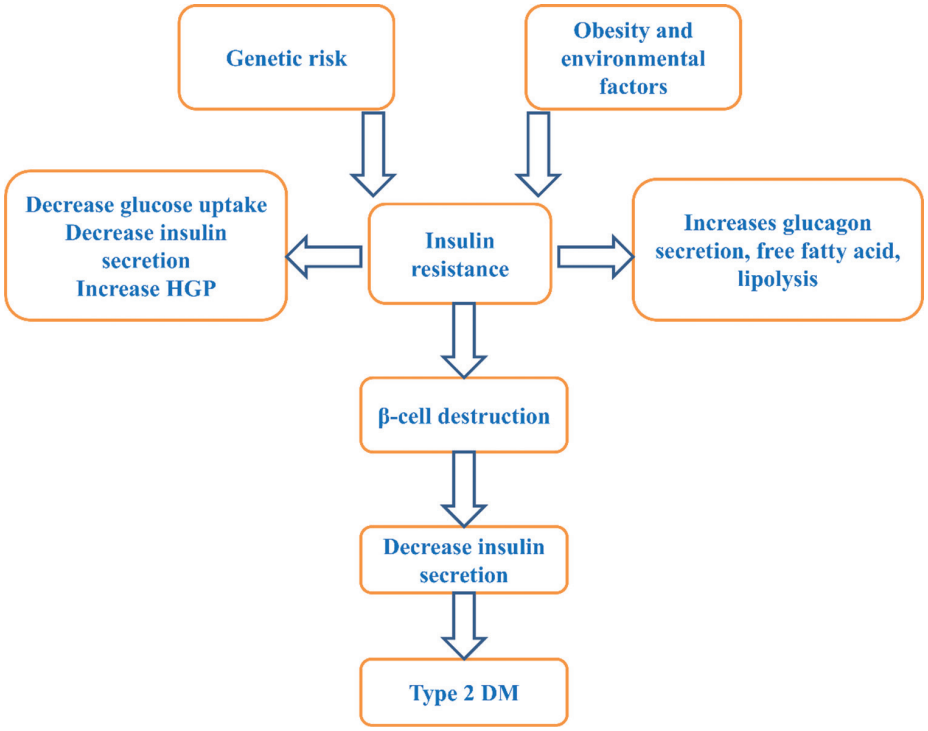

Figure 3. General pathophysiology of type 2 DM
Abbreviations: DM: Diabetes mellitus; HGP: Hepatic glucose production.

age of 25). The severity of the condition varies depending on the specific gene mutation involved.[29,30]

4. Diagnosis and risk factors of diabetes

4.1. Diagnosis of diabetes

Early diagnosis of diabetes is crucial for preventing severe complications. Common diagnostic tests include glycosylated hemoglobin (HbA1c), which reflects average blood glucose over the past 2 – 3 months (≥6.5% indicates diabetes). The oral glucose tolerance test (OGTT) is another widely used diagnostic method in which a plasma glucose level of ≥11.1 mmol/L 2 h after ingesting 75 g of glucose confirms diabetes. In addition, fasting plasma glucose (≥7.0 mmol/L indicates diabetes) and random blood glucose tests (≥11.1 mmol/L with symptoms indicate diabetes) are widely used.[31] Various diagnostic tests and their criteria are summarized in Table 2.

4.2. Risk factors of diabetes

Diabetes is influenced by a combination of genetic, lifestyle, and environmental factors, making the identification of risk factors crucial for effective prevention and targeted interventions.

(i) Type 1 DM risk factors:
The development of T1DM is associated with genetic pre-disposition (family history, candidate genes), infectious factors (seasonality, viral infections, enteroviruses), and nutritional influences (maternal diet, breastfeeding, cow's milk, and Vitamin D).[32]

(ii) Type 2 DM risk factors:
Risk factors for T2DM include obesity, family history, aging, ethnicity, physical inactivity, smoking, sleep disturbances, cardiovascular disease, dyslipidemia, hypertension, serum uric acid, and depression.[33]

(iii) GDM risk factors
Risk factors for GDM include a history of GDM, family history of T2DM, obesity, advanced maternal age, and specific ethnic background (African, Hispanic, and Asian). In addition, hypertension, insulin-resistant conditions (e.g., polycystic ovary syndrome), smoking, and pregnancy-related factors (e.g., macrosomia, glycosuria) contribute to increased risk.[34]

DM can lead to complications that affect multiple organ systems, significantly impairing patient health and quality of life.[35] Both microvascular and macrovascular complications, including retinopathy, neuropathy, and cardiovascular dysfunction, contribute to high morbidity and mortality rates.[36] About 40% of diabetic individuals develop diabetic nephropathy, making it the primary cause of chronic kidney disease globally.[37] DM induces end-stage renal disease primarily through kidney fibrosis, driven by diabetes-related mesenchymal activations, which promote

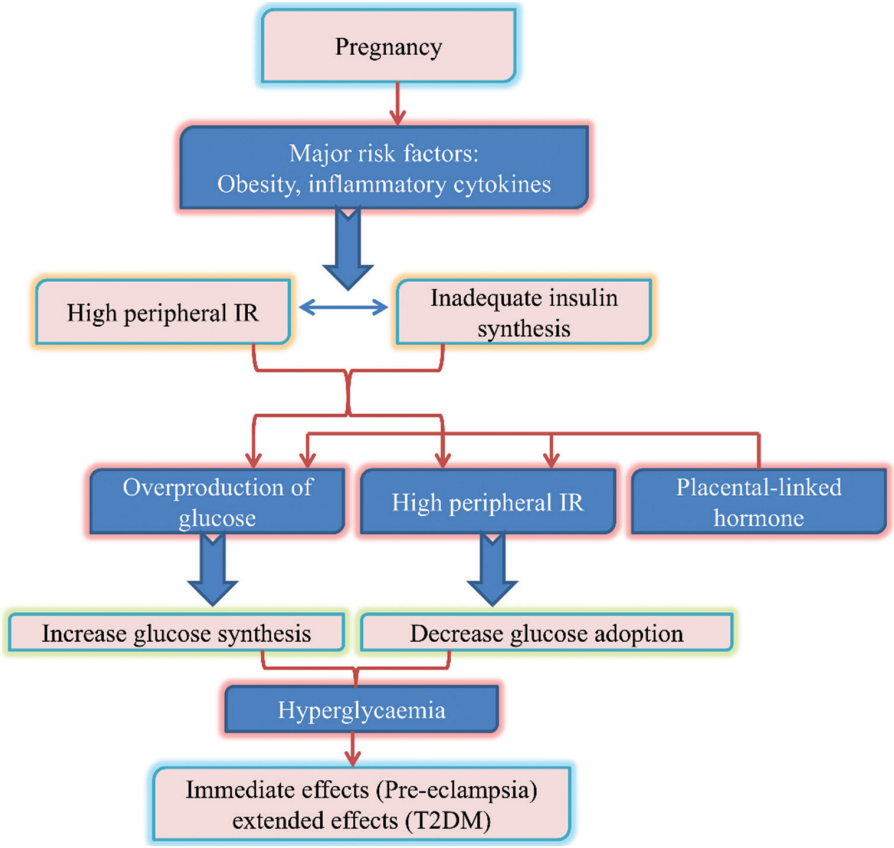

Figure 4. Pathophysiology of gestational diabetes mellitus
Abbreviations: IR: Insulin resistance; T2DM: Type 2 diabetes mellitus.

Table 2. Tests and their criteria for diabetes diagnosis

Test	Description	Diagnostic Criteria
Fasting plasma glucose	Determines blood glucose level after fasting for at least 12 h.	≥7.0 mmol/L
OGTT	Determines blood glucose 2 h after ingesting 75 g of glucose.	≥11.1 mmol/L
Glycosylated hemoglobin	Reflects average blood glucose levels over the past 2 – 3 months.	≥48 mmol/mol (≥6.5%)
Random blood glucose test	Monitors blood sugar levels at any time of day, regardless of meal timing.	≥11.1 mmol/L with symptoms of diabetes
Impaired glucose tolerance	Identified through OGTT when plasma glucose levels are elevated but not high enough for diabetes.	7.8 – 11.0 mmol/L after 2 h of ingesting 75 g glucose

Abbreviation: OGTT: Oral glucose tolerance test

extracellular matrix (ECM) synthesis and deposition.[38] In addition, the accumulation of ECM components, such as collagens, inflammatory cells, and dysregulated cytokine and chemokine activity contributes to organ fibrosis in individuals with diabetes.[39]

4.3. Therapeutic potential of plant-based compounds in diabetes

The interplay of oxidative stress, chronic inflammation, and metabolic dysregulation in diabetes highlights the therapeutic potential of plant-derived bioactive compounds. Polyphenols, flavonoids, and other phytochemicals exhibit anti-inflammatory, antioxidant, and insulin-sensitizing properties, offering promising alternatives to conventional therapies. The subsequent sections will explore how these compounds mitigate key diabetes-related risk factors and complications.[40]

5. Various therapies in the management of diabetes

5.1. Medical nutrition therapy (MNT)

MNT is provided by a registered dietitian nutritionist and encompasses nutrition diagnosis and counseling

services. It plays a crucial role in diabetes education and management.[41,42] The optimization of MNT for DM remains an area of ongoing research, particularly concerning energy content, macronutrient distribution, and quantity.[42] While MNT aims to develop diet plans that are both evidence-based and patient-centered, concerns have been raised regarding its ability to balance medical efficacy with patient preferences. Therefore, collaboration between diabetologists and registered dieticians is essential to establish evidence-based nutritional guidelines for MNT in preventing and managing diabetes and its complications.[43]

5.2. Stem cell therapy

Stem cell research holds great promise for DM management.[44] Stem cell therapy aims to restore β-cell function by replacing dysfunctional pancreatic cells with multipotent stem cells. Various techniques have been developed to generate β-cell substitutes or restore β-cell functionality using different stem cell sources, such as induced pluripotent stem cells, embryonic stem cells, and adult stem cells.[45,46]

5.3. Oral hypoglycemic agents

Oral hypoglycemic agents are widely used in the treatment of T2DM. These agents include biguanides, sulfonylureas, meglitinides, thiazolidinediones, dipeptidyl peptidase (DPP)-4 inhibitors, odium-glucose cotransporter 2 inhibitors, and α-glucosidase inhibitors (Table 3). Biguanides, such as metformin, reduce hepatic glucose production and enhance insulin sensitivity, although they can cause gastrointestinal discomfort and, in rare cases, lactic acidosis. Sulfonylureas (e.g., glimepiride) and meglitinides (e.g., repaglinide) stimulate insulin secretion from pancreatic β-cells but are linked to hypoglycemia and weight gain. Thiazolidinediones (e.g., pioglitazone) improve insulin sensitivity but may lead to weight gain, fluid retention, and heart failure. DPP-4 inhibitors (e.g., sitagliptin) enhance insulin release with a low risk of hypoglycemia, although they may cause joint pain and pancreatitis.[47]

Table 3. Treatment and management strategies for diabetes

Drug category	Drug name	Mechanism of action	Side effects	References
Rapid-acting insulin	Insulin lispro, insulin aspart, insulin glulisine, technosphere Insulin	Acts by directly binding to its receptors on the plasma membranes of the cells, leading to a cascade of intracellular events that facilitate glucose uptake and metabolism	Hypoglycemia, weight gain, electrolyte disturbances, lip dystrophy, peripheral hyperinsulinemia	48,49
Short-acting	Regular human insulin			
Intermediate	NPH human insulin			
Long-acting	Insulin detemir, insulin glargine, insulin glargine-yfgn, insulin degludec			
Insulin secretagogues	Sulfonylurea (glimepiride, repaglinide, glipizide)	Suppress the β-cell K^+ATP channel and promote the release of insulin	Hypoglycemia, weight gain	50
	Meglitinides (nateglinide, glyburide)			
GLP-1 agonists	Liraglutide, exenatide, lixisenatide	Reduce glucagon secretion, increase glucose-dependent insulin secretion, and post-pone gastric emptying	Pancreatitis	51,52
α-glucosidase inhibitors	Acarbose, miglitol, voglibose	Lower the rate at which glucose is absorbed from carbohydrates by slowing down their breakdown in the gut	Abdominal pain, diarrhea, flatulence	53
Sodium-glucose cotransporter 2 inhibitors	Canagliflozin, dapagliflozin, empagliflozin	Raise the excretion of glucose in urine	Urinary tract infection, hypotension	54
Dipeptidyl peptidase 4 (DPP4 inhibitors)	Vildagliptin, Linagliptin, Saxagliptin, Sitagliptin	Raises levels of endogenous GLP-1 and glucose-dependent insulinotropic polypeptide	Respiratory tract infection, nasopharyngitis, headache	55,56
Biguanides	Metformin	Reduce insulin resistance and glucose generation by activating AMP-activated protein kinase	Gastrointestinal irritation, lactic acidosis	57
Thiazolidinediones	Pioglitazone, Rosiglitazone	Activate peroxisome proliferator-activated receptors to reduce insulin resistance	Fluid retention, weight gain	58

Abbreviation: GLP-1: Glucagon-like peptide 1.

5.4. Gene therapy

Gene therapy addresses diseases caused by defective genes by introducing a functional gene into affected cells. This approach offers a potential long-term solution for various conditions across multiple medical fields.[59,60] Gene therapy is categorized into somatic and germline therapy. Somatic gene therapy targets diseased somatic cells, whereas germline gene therapy involves genetic modifications in reproductive cells, thereby preventing the transmission of genetic disorders to future generations.[61] The increasing application of gene therapy is driven by its potential to treat complex diseases, such as DM, autoimmune disorders, cardiovascular diseases, and cancers, which are often difficult to manage with conventional treatments.[62]

5.5. Nanotechnology

Nanotechnology has significantly advanced diabetes management by improving glucose monitoring and insulin delivery systems. It facilitates non-invasive insulin administration and enhances the effectiveness of cell- and gene-based therapies for T1DM.[63,64] In addition, early and precise disease diagnosis is crucial for preventing complications and minimizing treatment delays, and nanotechnology plays a pivotal role in achieving this objective.[65]

5.6. Lifestyle modification

Lifestyle modifications play a fundamental role in diabetes management. Patients should adopt a diet rich in vegetables, fruits, and whole grains while selecting non-fat dairy products and lean proteins. In addition, reducing the intake of sugary and high-fat foods is essential for maintaining a balanced diet. Quitting smoking and limiting alcohol consumption are also key behavioral changes that can improve overall health.[66,67] Lifestyle interventions should be personalized to meet individual patient needs. Furthermore, diabetes self-management can be effectively supported through web-based strategies.[68]

5.7. Medicinal plants

Medicinal plants have been widely explored for the treatment of DM due to their natural bioactive compounds, which help regulate blood glucose levels (Table 4). Several plants, including *Gymnema sylvestre*, *M. charantia* (bitter melon), and *Trigonella foenum-graecum* (fenugreek), have shown promising hypoglycemic effects. These plants enhance insulin secretion, improve glucose metabolism, and reduce oxidative stress, making them potential complementary therapies for diabetes management.[69]

5.7.1. Momordica charantia L.

M. charantia L., commonly known as bitter gourd, karela, or balsam pear, belongs to the Cucurbitaceae family. It has been traditionally used as an adjunct or alternative treatment for diabetes due to its rich composition of bioactive compounds, including amino acids, flavonoids, glycosides, and vitamins. These components exhibit antioxidant, anti-inflammatory, immunomodulatory, and anti-hyperglycemic effects, improving insulin sensitivity and reducing hepatic glucose production to help regulate blood glucose levels effectively (Figure 5).[70,71] Studies indicate that hypoglycemic herbs improve insulin secretion, boost glucose uptake by skeletal muscle or adipose tissues, and inhibit hepatic glucose production and intestinal glucose absorption.[72] The main bioactive compounds responsible for bitter melon's antidiabetic effects are charantin and polypeptide-p. Charantin is a combination of 5,22-stigmasterol glucoside and β-sitosterol glucoside, two steroidal saponins. Charantin has been shown to lower blood glucose levels by promoting glucose absorption and glycogen synthesis in the liver, muscle, and adipose tissues. Polypeptide-p, also referred to as p-insulin, is a bioactive peptide that functions similarly to human insulin. Polypeptide-p has shown hypoglycemic effects, suggesting its potential as a plant-based insulin substitute, especially for individuals with T1DM.[73]

5.7.2. Allium sativum L.

A. sativum (garlic), a member of the Liliaceae family, contains key bioactive compounds such as allicin, diallyl disulfide, and diallyl trisulfide, along with flavonoids and saponins. These compounds exhibit various pharmacological properties, including hypoglycemic, antioxidant, and anti-inflammatory effects, making garlic a beneficial supplement for diabetes management and metabolic health.[74] In the context of diabetes treatment, garlic has been shown to upregulate the gene expression of caspase-3 and caspase-9, which are involved in apoptosis regulation. In addition, garlic has been demonstrated to reduce the levels of pro-inflammatory cytokines, including interleukin (IL)-1β, IL-6, and tumor necrosis factor-alpha, while simultaneously increasing interferon-gamma, both in *in vitro* and *in vivo* studies.[75] The bioactive sulfur compound allicin has been shown to enhance insulin secretion and improve insulin sensitivity, leading to better blood glucose control. Other sulfur-containing compounds, such as allixin, vinyldithiins, and ajoene, may also contribute to garlic's antidiabetic properties. These compounds exhibit a range of biological effects, such as anti-inflammatory and antioxidant properties, which are thought to play a role in diabetes regulation.[76]

5.7.3. Morus alba L.

M. alba (white mulberry) is a fast-growing deciduous plant native to China, Japan, and India. Historical sources

Table 4. Medicinal plants with antidiabetic activity and their mechanisms of action

No.	Common name	Botanical name	Family	Plant part used	Mechanism of action
1	Bitter melon	*Momordica charantia*	Cucurbitaceae	Fruit	Increases insulin secretion, enhances glucose uptake
2	Fenugreek	*Trigonella foenum-graecum*	Fabaceae	Seeds	Increases insulin secretion, delays carbohydrate absorption
3	Aloe vera	*Aloe barbadensis*	Asphodelaceae	Leaf gel	Improves insulin sensitivity, reduces fasting blood glucose
4	Holy basil (Tulsi)	*Ocimum sanctum*	Lamiaceae	Leaves	Enhances insulin secretion, reduces oxidative stress
5	Cinnamon	*Cinnamomum verum*	Lauraceae	Bark	Enhances insulin sensitivity, inhibits α-glucosidase
6	Garlic	*Allium sativum*	Amaryllidaceae	Bulb	Increases insulin secretion, reduces oxidative stress
7	Onion	*Allium cepa*	Amaryllidaceae	Bulb	Enhances insulin secretion, reduces blood glucose
8	Indian gooseberry (Amla)	*Phyllanthus emblica*	Phyllanthaceae	Fruit	Reduces glucose absorption, enhances insulin secretion
9	Curry leaves	*Murraya koenigii*	Rutaceae	Leaves	Delays carbohydrate absorption, enhances insulin function
10	Guava	*Psidium guajava*	Myrtaceae	Leaves	Reduces glucose absorption, increases insulin sensitivity
11	Gymnema (Gurmar)	*Gymnema sylvestre*	Apocynaceae	Leaves	Inhibits glucose absorption, regenerates pancreatic β-cells
12	Neem	*Azadirachta indica*	Meliaceae	Leaves	Enhances insulin sensitivity, reduces glucose absorption
13	Jamun (Indian Blackberry)	*Syzygium cumini*	Myrtaceae	Seeds	Enhances insulin secretion, reduces blood glucose
14	Berberis (Daru Haldi)	*Berberis aristata*	Berberidaceae	Root bark	Inhibits α-glucosidase, enhances insulin secretion
15	Clove	*Syzygium aromaticum*	Myrtaceae	Buds	Enhances insulin secretion, reduces oxidative stress
16	Black pepper	*Piper nigrum*	Piperaceae	Seeds	Improves insulin sensitivity, reduces glucose absorption
17	Turmeric	*Curcuma longa*	Zingiberaceae	Rhizome	Reduces oxidative stress, enhances insulin sensitivity
18	Ginger	*Zingiber officinale*	Zingiberaceae	Rhizome	Increases glucose uptake, reduces insulin resistance
19	Flaxseed	*Linum usitatissimum*	Linaceae	Seeds	Reduces glucose absorption, improves insulin sensitivity
20	Indian kino (Vijaysar)	*Pterocarpus marsupium*	Fabaceae	Bark	Regenerates pancreatic β-cells, enhances insulin secretion
21	Moringa (Drumstick)	*Moringa oleifera*	Moringaceae	Leaves	Enhances insulin secretion, reduces glucose absorption
22	Green tea	*Camellia sinensis*	Theaceae	Leaves	Reduces glucose absorption, improves insulin sensitivity
23	Black tea	*Camellia sinensis*	Theaceae	Leaves	Enhances insulin action, reduces blood glucose
24	Curry plant	*Helichrysum italicum*	Asteraceae	Leaves	Reduces glucose absorption, improves insulin action
25	Cumin	*Cuminum cyminum*	Apiaceae	Seeds	Enhances insulin sensitivity, reduces oxidative stress
26	Basil	*Ocimum basilicum*	Lamiaceae	Leaves	Enhances insulin secretion, reduces blood glucose
27	Coriander	*Coriandrum sativum*	Apiaceae	Leaves & seeds	Increases insulin secretion, reduces blood glucose
28	Oregano	*Origanum vulgare*	Lamiaceae	Leaves	Improves insulin action, reduces blood glucose
29	Rosemary	*Rosmarinus officinalis*	Lamiaceae	Leaves	Enhances insulin sensitivity, reduces oxidative stress
30	Sage	*Salvia officinalis*	Lamiaceae	Leaves	Improves insulin function, reduces glucose absorption
31	Thyme	*Thymus vulgaris*	Lamiaceae	Leaves	Enhances insulin sensitivity, reduces oxidative stress
32	Bay leaf	*Laurus nobilis*	Lauraceae	Leaves	Enhances insulin action, reduces blood glucose
33	Indian barberry	*Berberis asiatica*	Berberidaceae	Root bark	Inhibits α-glucosidase, enhances insulin secretion
34	Licorice	*Glycyrrhiza glabra*	Fabaceae	Root	Enhances insulin function, reduces oxidative stress
35	Saffron	*Crocus sativus*	Iridaceae	Stigma	Reduces oxidative stress, improves insulin action
36	Ashwagandha	*Withania somnifera*	Solanaceae	Root	Enhances insulin sensitivity, reduces stress-related glucose levels

(Cont'd...)

Table 4. ***(Continued)***

No.	Common name	Botanical name	Family	Plant part used	Mechanism of action
37	Bael	*Aegle marmelos*	Rutaceae	Leaves	Improves insulin function, reduces blood glucose
38	Ginseng	*Panax ginseng*	Araliaceae	Root	Enhances insulin secretion, reduces glucose absorption
39	Shatavari	*Asparagus racemosus*	Asparagaceae	Root	Enhances insulin secretion, reduces oxidative stress
40	Hibiscus	*Hibiscus rosa-sinensis*	Malvaceae	Flowers	Reduces oxidative stress, improves insulin action
41	Indian Costus	*Saussurea lappa*	Asteraceae	Root	Enhances insulin action, reduces blood glucose
42	Barley	*Hordeum vulgare*	Poaceae	Seeds	Improves insulin resistance, lowers glucose absorption
43	Wheatgrass	*Triticum aestivum*	Poaceae	Leaves	Reduces oxidative stress, enhances glucose metabolism
44	Pumpkin	*Cucurbita maxima*	Cucurbitaceae	Seeds	Enhances insulin secretion, reduces blood glucose
45	Papaya	*Carica papaya*	Caricaceae	Leaves	Improves pancreatic function, reduces blood glucose
46	Mulberry	*Morus alba*	Moraceae	Leaves	Inhibits carbohydrate digestion, enhances insulin function
47	Blueberry	*Vaccinium corymbosum*	Ericaceae	Fruit & Leaves	Reduces oxidative stress and improves insulin function
48	Black plum	*Eugenia jambolana*	Myrtaceae	Seeds & Bark	Enhances insulin secretion, reduces blood glucose
49	Prickly pear cactus	*Opuntia ficus-indica*	Cactaceae	Pads	Reduces glucose absorption, improves insulin sensitivity
50	Chicory	*Cichorium intybus*	Asteraceae	Root	Inhibits glucose absorption, enhances insulin sensitivity

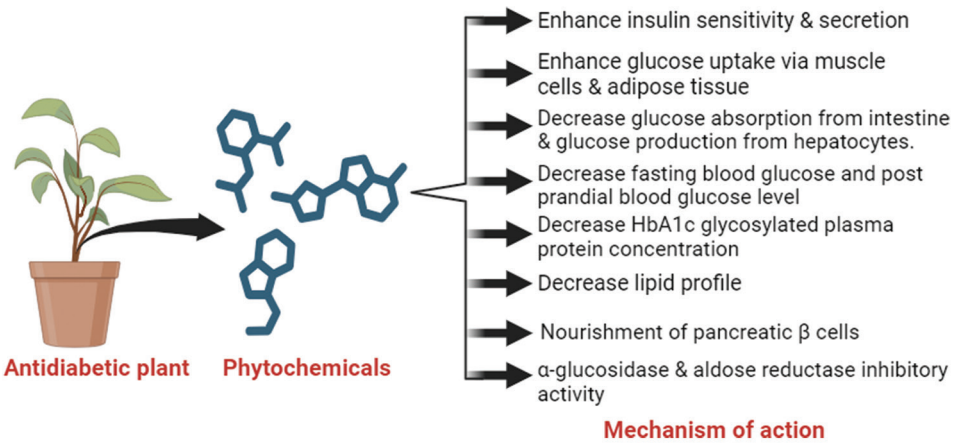

Figure 5. Mechanism of action of antidiabetic medicinal plants

indicate that its fruits, leaves, and bark have been utilized in traditional medicine since around 3,000 BCE. Mulberry leaves are rich in essential nutrients, including proteins, lipids, carbohydrates, fiber, β-carotene, xanthophylls, Vitamins C and E, β-sitosterol, and several important minerals. Notably, the bioactive compounds present in mulberry exhibit significant antidiabetic properties, particularly through their ability to inhibit the activity of α-amylase and α-glucosidase, enzymes that help in controlling blood glucose levels.[77] While the precise mechanisms by which mulberry exerts its hypoglycemic effects are still under investigation, prior research has demonstrated its potent α-glucosidase inhibitory activity. This suggests that mulberry extracts may also contribute to enhanced insulin secretion and improved insulin sensitivity.[78]

5.7.4. Trigonella foenum-graecum L.

T. foenum-graecum (fenugreek) is an annual herb native to the Mediterranean, India, and China. It produces small, fine seeds that are rich in galactomannans, mucilaginous polysaccharides, and proteins, including tryptophan and lysine. The leaves of fenugreek contain a variety of bioactive compounds, such as free amino acids (e.g., 4-hydroxyisoleucine and histidine), fats, steroid saponins,

trigonelline, coumarins, flavonoids, sterols, lecithin, choline, nicotinic acid, and essential minerals. In addition, fenugreek is a rich source of β-carotene, ascorbate, iron, calcium, and zinc. Among the most bioactive polyphenols found in fenugreek, rhaponticin, and isovitexin have been identified as key contributors to its antiglycemic effects. The hypoglycemic properties of fenugreek arise from the synergistic action of its diverse chemical components. Fenugreek seed galactomannans, in particular, help in delaying gastric emptying, slowing carbohydrate absorption, and modulating glucose transport. This effect is particularly pronounced when fenugreek is consumed in the form of pap-based preparation.[77]

5.7.5. Zingiber officinale Rosc.

Z. officinale (ginger) is an herbaceous plant with a solid rhizome belonging to the Zingiberaceae family. The rhizome is rich in essential oils, containing monoterpenes such as phellandrene, camphene, 1,8-cineole, geranial, citral, terpineol, and borneol, as well as sesquiterpenes, including ar-curcumen, α-zingiberene, β-sesquifelandrene, β-bisabolene, and zingiber.[79] Ginger has demonstrated antidiabetic effects by increasing insulin sensitivity, protecting pancreatic β-cells, and reducing oxidative stress. The main bioactive compounds responsible for its antidiabetic effects are shogaol and gingerol.[80] Studies suggest that ginger enhances insulin sensitivity by facilitating glucose uptake and utilization in peripheral tissues. In addition, it may stimulate insulin secretion.[81] Ginger extracts have also been shown to exhibit α-glucosidase inhibitory activity, which may contribute to delayed carbohydrate digestion and glucose absorption in the intestine.[82]

5.7.6. Cinnamomum zeylanicum J. Presl

C. zeylanicum (Ceylon cinnamon) is native to Sri Lanka (formerly Ceylon) but is now cultivated in several regions of South Asia and North America. The primary constituents of its essential oils include cinnamaldehyde, cinnamyl acetate, eugenol, and β-caryophyllene. The bark of Ceylon cinnamon contains polysaccharides, phenolic acids such as cinnamic acid and its derivatives, oligomeric proanthocyanidins, and diterpenes.[83] Cinnamon has been shown to enhance insulin sensitivity in insulin-dependent tissues by modulating cellular signaling pathways, promoting glucose transporter type (GLUT)-4 translocation, and increasing glucose uptake.[84]

5.7.7. Panax ginseng C. A. Meyer

P. ginseng (ginseng), a member of the Araliaceae family, has been utilized in traditional medicine for centuries. It is native to the Central Himalayas in China and extends through Korea, Japan, and North America.[85] The primary bioactive compounds, such as triterpene saponins, panaxosides, and ginsenosides, boost mental and physical performance and exhibit antistress effects. In addition, ginseng contains polysaccharides, peptidoglycans (panaxans A–U), polyacetylenes, essential oils, sesquiterpene alcohols, sterols, flavonols, and phenolic acids. It has been proposed as a potential treatment for diabetes by upregulating the expression of GLUT-1 and GLUT-4, thereby enhancing glucose uptake.[86]

5.7.8. Beta vulgaris L.

B. vulgaris (beetroot), a member of the Chenopodiaceae family, can grow up to 120 cm in height.[87] It has been traditionally used in Turkish medicine for managing diabetes. Beetroot contains various phytoconstituents, such as betalains, flavonoids (quercetin, rutin, apigenin, kaempferol, and ferulic acid derivatives), and saponins, which exhibit antidiabetic activity. The hypoglycemic effects of beetroot are attributed to its ability to stimulate insulin secretion and enhance glucose uptake in peripheral tissues. Moreover, its antioxidant and anti-inflammatory properties may help prevent diabetes-related complications.[88] Beetroot extract (aqueous fraction) has been shown to activate signaling pathways involving acetylcholine and GLP-1, thereby increasing insulin secretion in response to glucose, a mechanism known as glucose-stimulated insulin secretion. In addition, the upregulation of GLUT-4 transporters on the cell membrane facilitates glucose transport into cells, further improving glucose uptake.[89]

5.7.9. Chenopodium ambrosioides L.

C. ambrosioides (Mexican tea) is a perennial shrub that can grow up to 1 m in height and belongs to the Chenopodiacea family.[90] This plant contains several phytoconstituents, such as alkaloids, flavonoids, and saponins, which contribute to its medicinal properties. Its hypoglycemic effects are primarily attributed to the stimulation of insulin secretion and the enhancement of glucose uptake.[90] Studies have demonstrated that Mexican tea exhibits hypoglycemic and antihyperglycemic effects on experimental models, particularly in rats. However, the specific metabolic pathways underlying these effects remain unexplained. While the aqueous extract of Mexican tea has been shown to significantly reduce fasting blood glucose levels, further research is needed to elucidate its precise molecular targets and metabolic mechanisms.[91]

6. Limitations

Although pre-clinical and *in vitro* research on a variety of medicinal plants has demonstrated promising antidiabetic effects, several limitations must be acknowledged. *In vitro*

studies, for instance, are valuable for identifying potential mechanisms of action. However, they may not fully replicate the intricate physiological interactions that occur in living organisms. These studies often concentrate on specific molecular targets or pathways, overlooking the fact that diabetes is a multifaceted condition affecting multiple organs and systems. Furthermore, although animal models provide useful insights, they may not accurately represent the pathophysiology of diabetes in humans. Laboratory animals are typically maintained on standardized diets and have limited physical activity, which does not reflect the diverse lifestyles and environmental exposures of human populations. These factors can significantly influence disease progression and treatment efficacy. Moreover, diabetes-induced in animals through chemical or genetic manipulation may not fully capture the pathophysiological complexity of human diabetes, especially T2DM, which involves insulin resistance, impaired insulin secretion, and genetic pre-disposition. Another challenge in the field is the variability in extract preparation, dosage, and treatment duration, which can make it difficult to compare study outcomes across different investigations. Finally, further research is required to assess the long-term safety and effectiveness of various medicinal plants in human populations.

7. Conclusion

DM is a complex and widespread health challenge that requires a multifaceted approach for effective management. With distinct classifications, such as T1DM, T2DM, GDM, and MODY, each form necessitates tailored clinical strategies. Early and accurate diagnosis through HbA1c testing, fasting plasma glucose measurement, and OGTT test is crucial for timely intervention. While conventional treatments such as insulin therapy, oral hypoglycemic agents, and lifestyle modifications remain the cornerstone of diabetes management, emerging innovations – including gene therapy, nanotechnology, and stem cell research – offer promising advancements. In addition, medicinal plants such as *G. sylvestre*, *M. charantia*, and *T. foenum-graecum* present valuable complementary therapeutic potential.

A holistic strategy that integrates prevention, early diagnosis, and innovative treatments is critical in tackling the global diabetes epidemic. Public health initiatives should emphasize education, lifestyle interventions, and equitable access to healthcare to reduce diabetes prevalence and associated complications. Furthermore, the integration of artificial intelligence-driven technologies and digital therapeutics enhances self-management and personalized care, empowering patients to take an active role in disease control. By combining scientific advancements with traditional medicine, healthcare systems can develop more effective and sustainable strategies to improve diabetes outcomes and overall public health.

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Conflict of interest

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Author contributions

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ACCSCIENCE PUBLISHING

Innovative Medicines & Omics

REVIEW ARTICLE

Neuroinflammation and progress in clinical trials for the treatment of Alzheimer's disease and related dementias: An update

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(This article belongs to the *Special Issue: Alzheimer Disease and Other Forms of Dementias - Current Research Progress and Drug Development*)

Abstract

According to the latest report in 2024 by the World Health Organization, based on global data from 2021, Alzheimer's disease (AD) and other forms of dementia rank seventh among the leading causes of death worldwide, with an estimated 1.8 million deaths. This alarming number underscores the urgent requirement for effective treatments. AD and other dementias also severely affect the global economy. Unfortunately, no cure has been found, and effective treatments remain limited. Over the past two decades, thousands of disease-modifying drugs have been developed for AD treatment. However, most have failed to progress beyond phase I clinical trials, with only a few reaching phase III. To date, lecanemab (sold under the brand name Leqembi) is the only drug to receive full approval from the United States Food and Drug Administration for slowing AD progression. This drug is specifically designed to target and clear amyloid-beta (Aβ) plaques. Apart from targeting Aβ aggregation and tau tangles, neuroinflammatory regulatory pathways have emerged as promising therapeutic targets. With advancing research, neuroinflammation has been considered one of the core characteristics of AD and the third major pathological hallmark of the disease after Aβ plaques and neurofibrillary tau tangles. In this review, we summarize key research findings in neuroinflammatory regulation of AD and related dementias that are promising for treatments. We also provide an overview of clinical trials targeting the immune system or neuroinflammatory regulatory pathways, analyzing their challenges and potential successes.

Keywords: Alzheimer's disease and related dementias; Immune system dysregulation; Neuroinflammation; Amyloid-beta plaques; Tau tangles; Clinical trials

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1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease, and it is the most common cause of dementia, with 60 – 80% of cases occurring among elderly

people.[1] Dementia is manifested by a decline in memory, language skills, problem-solving abilities, spatial and temporal awareness, and judgment.[2-6] Over the past three decades, the number of deaths caused by AD and related dementias (RD) has increased from 0.56 million in 1990 to 1.62 million in 2019.[7] A recent report revealed that 6.7 million Americans – equivalent to 1 in 9 individuals aged 65 and older – are affected by AD.[8] AD and RD together are the seventh leading cause of death globally.[7,9-11] These diseases have a direct impact on both global health and the economy. Around 83% of AD caregivers are unpaid family members, friends, or others.[12] If compensated, their collective contribution would amount to approximately 339.5 billion USD, according to the estimated cost of care in 2022. The lifetime care cost for an individual with dementia was estimated to be 392,874 USD in 2022, with unpaid family caregivers shouldering 70% of this burden, including food and medications.[2,13] Over the years, with the increased understanding of the regulatory mechanisms underlying AD pathology, several drugs have been developed and tested in clinical trials. However, finding an effective cure or treatment remains challenging due to the complex pathogenesis of the disease.[14-16] At present, available drugs for AD treatments provide only moderate benefits, primarily by slowing the progression of the disease.

At present, no drug or medication can reverse, halt, or cure AD. The only drug officially approved by the United States Food and Drug Administration (US FDA) is lecanemab, which only moderately slows AD progression by clearing amyloid-beta (Aβ) plaques.[17] Most drug development efforts and clinical trials thus far have primarily focused on clearing Aβ plaques and neurofibrillary tau tangles in the brain. However, there is a growing shift toward targeting the pathological mechanisms responsible for the accumulation of Aβ plaques and neurofibrillary tau tangles, rather than directly targeting them. In addition, several other pathways that link to the disease are now receiving increased attention. Aβ plaques and neurofibrillary tau tangles have long been recognized as hallmark pathological features of AD, and recent research has identified neuroinflammation as the third pathological hallmark. Numerous studies have provided substantial evidence suggesting that inflammatory pathways play a crucial role in the pathogenesis of AD and RD.[18-25] These studies have led to the acknowledgment of neuroinflammation as an important pathological hallmark of AD.

In this review, we aim to highlight the critical role of neuroinflammation in AD and RD, providing a comprehensive summary of immune system dysregulation and its connection to neuroinflammation and AD and RD. Then, we will discuss clinical trials targeting the immune system as a potential therapeutic approach for treating AD patients. Despite the extensive efforts, most drugs have failed in phase 1 clinical trials, with several of them being discontinued in phase II and only a few advancing to phase III trials. We will analyze the reasons behind these failures and discuss promising strategies for achieving success. Over 3,300 clinical trials have been conducted on AD, involving a variety of drug candidates (clinicaltrials.gov),[26,27] but only three drugs have reached the final stages of development. Of these, only lecanemab (Leqembi) has been approved by the US FDA, aducanumab (Aduhelm) is in the approval process, and donanemab is also undergoing US FDA review.[17]

2. Immune system dysregulation and neuroinflammation in AD and RD

2.1. Neuroinflammation as a key factor

Under normal conditions, neuroinflammation plays a crucial role in protecting the brain against the infiltration or infection of pathogens. However, in unfavorable or prolonged circumstances, neuroinflammation can lead to various severe neurological conditions, including AD, Parkinson's disease (PD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD). These conditions reveal that the pathways linking neuroinflammation to neurodegeneration are distributed across various regions of the central nervous system (CNS).[27] Over the years, a vast number of research has demonstrated the presence of prolonged immune responses in the brains of AD patients. In such a chronic immune response, sustained neuroinflammation becomes detrimental, perpetuating a cycle of neuronal damage and degeneration in the CNS. As research has advanced, neuroinflammation is increasingly recognized as a core contributing factor to the progression of AD and RD. Indeed, neuroinflammation is now considered the third pathological hallmark of AD, alongside Aβ plaques and tau tangles.[28] Importantly, it has been well documented that neuroinflammation exacerbates the severity of the disease by worsening Aβ and tau pathologies.[29,30] This highlights the crucial role neuroinflammation plays in the aggregation of toxic Aβ plaque and tau tangles, leading to disease progression, making neuroinflammation a promising target for the treatment of AD and RD. Moreover, neuroinflammation is not only implicated in AD but has been identified as a key factor in the dysregulation of many neurological diseases, continuously emerging as a potential mediator of cognitive deficits. Therefore, there is an urgent need to explore neuroinflammatory pathways as potential drug targets and advance them through clinical trials to develop effective treatments for AD and RD.

2.2. Chronic neuroinflammation

Chronic neuroinflammation is characterized by excessive activation of glial cells, including microglia and astrocytes. Activated microglia release pro-inflammatory cytokines (such as interleukin-1 beta, interleukin-6, tumor necrosis factor-alpha, and interferon-gamma), chemokines (such as C-X-C motif chemokine ligands and CC chemokine ligands), and reactive oxygen species (such as inducible nitric oxide synthase, superoxide, nitric oxide, and peroxynitrite), all of which, if persistently expressed, contribute to neuronal damage and progressive neurodegeneration, as observed in AD, PD, HD, and MS.[31] Importantly, microglia also express anti-inflammatory markers, such as arginase-1, chitinase-like-3 protein 1, mannose receptor C-type 1, interleukin-10, Fc-gamma receptor I, transforming growth factor-beta 1, and sphingosine kinase 1.[31] Prolonged activation of resident macrophages (such as microglia) and other immune cells in the brain aggravates both Aβ and tau pathology.[28] Similarly, activated astrocytes release pro-inflammatory interleukin-1 beta, interleukin-6, tumor necrosis factor-alpha, and nitric oxide, while they also secrete several beneficial neurotrophic factors and thrombospondins.[31,32] Notably, astrocytes can switch their phenotype and proliferate in response to harmful conditions, leading to the formation of reactive astrocytes, a process known as reactive astrogliosis. Reactive astrogliosis has been observed in various pathological conditions, including intracranial infections, hypoxic-ischemic injury, AD, and epilepsy.[31,32] These findings underscore the profound impact of immune system dysregulation on chronic neuroinflammation in AD and RD, highlighting microglia and astrocyte-mediated neuroinflammation as important therapeutic targets.

Neuroinflammation also increases with aging and neurodegeneration. Age-related changes in neuroinflammation may accelerate the progression of cognitive impairment through glial activation, increased production of pro-inflammatory cytokines, and abnormal neuronal signaling, magnifying deterioration of the CNS microenvironment.[33,34] Apart from AD, dementia is also a clinical symptom in several other neurological diseases associated with neuroinflammation, such as vascular dementia, dementia with Lewy Bodies, frontotemporal dementia, Wernicke–Korsakoff syndrome, PD, ALS, and HD.[35-40] Both innate and adaptive immune system dysregulation are implicated in the pathogenesis of these diseases.[41-47] Microglia, astrocytes, and oligodendrocytes play a major role in innate immune system dysregulation, whereas the involvement of the adaptive immune system is evident from the presence of B and T lymphocytes in the post-mortem AD brain and the cerebrospinal fluid (CSF) of individuals with mild cognitive impairment (MCI) and AD patients.[42,48-52] Moreover, an increased frequency of helper T cells subsets, such as Th17 and Th9 lymphocytes, has been observed in AD patients.[53] These findings have driven the development of drugs targeting neuroinflammatory regulatory pathways as potential treatments to slow, halt, or reverse the progression of AD and RD. A graphical representation of immune system dysregulation in AD and RD, along with possible therapeutic targets, is presented in Figure 1A and B.

At present, several anti-neuroinflammatory drugs are undergoing phase III clinical trials, including hydralazine hydrochloride (ClinicalTrials.gov identifier: NCT04842552), xanomeline–trospium (KarXT, ClinicalTrials.gov identifier: NCT05511363), masitinib (ClinicalTrials.gov identifier: NCT05564169), NE3107 (ClinicalTrials.Gov identifier: NCT04669028), and spironolactone (ClinicalTrials.gov identifier: NCT04522739). In addition, sodium oligomannate capsule (GV-971), an anti-inflammatory drug that inhibits Aβ fibril formation, is also in clinical trials (ClinicalTrials.gov identifier: NCT05181475).

3. Drug candidates in clinical trials, challenges, and current progress for the treatment of AD and RD

3.1. Potential drugs for the treatment of AD and RD

Over the past two decades, several disease-modifying drugs have been developed for the treatment of AD, with approximately 2,700 clinical trials conducted since 2004. However, only a few have shown promising success rates in phase II and III trials.[54] A more recent report showed that over 3,300 clinical trials (clinicaltrials.gov) for AD treatment have been conducted.[26] Despite these efforts, the failure rate remains alarmingly high, estimated at approximately 99%,[54,55] meaning only 1% of drugs progress successfully through clinical trials. The few compounds that have demonstrated potential have primarily been designed for immunotherapy in AD patients. These notable compounds are aducanumab, lecanemab, donanemab, and oligomannate.[17,56-58] Aducanumab (brand name Aduhelm) is a monoclonal antibody designed to bind and eliminate aggregated Aβ plaques. Lecanemab (brand name Leqembi) is designed to reduce Aβ protofibrils in the brain and CSF. Donanemab (brand name Kisunla) is a humanized monoclonal antibody derived from mouse mE8-IgG2a antibody, specifically targeting Aβ (3-42) plaques. Oligomannate (also known as sodium oligomannate or GV-971) is a seaweed-derived oligosaccharide that reduces bacterial metabolite-driven peripheral infiltration of immune cells into the brain while also inhibiting Aβ

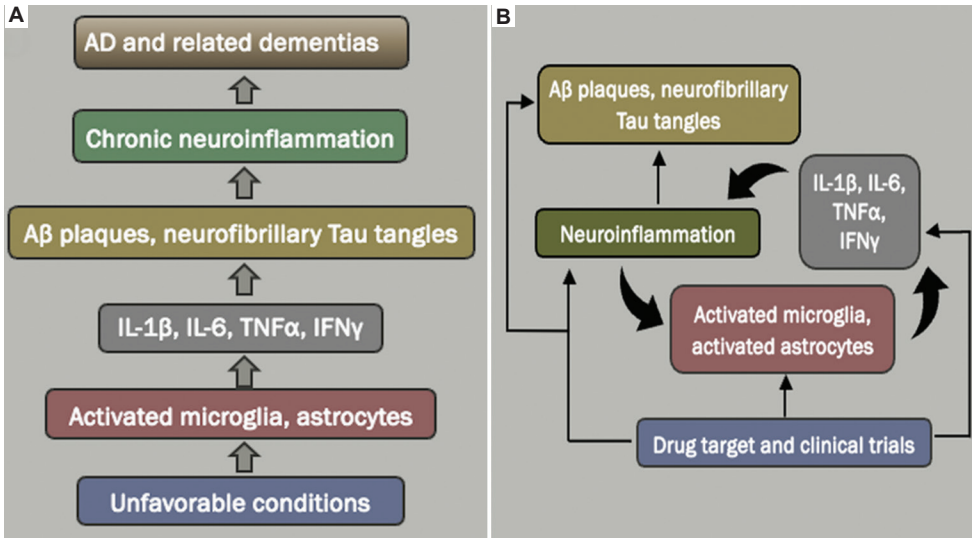

Figure 1. Neuroinflammatory pathways underlying AD and related dementias, and possible target sites for drug development and clinical trials. (A) Graphical representation of immune system dysregulation leading to Alzheimer's disease and related dementias. (B) Potential therapeutic targets. Abbreviations: Aβ: Amyloid-beta; AD: Alzheimer's disease; IFNγ: Interferon-gamma; IL-1β: Interleukin-1 beta; IL-6: Interleukin-6; TNFα: Tumor necrosis factor-alpha.

and tau formation. Despite their potential, the long-term effectiveness of these drugs remains uncertain. As of now, only lecanemab has been fully approved by the US FDA for AD treatment on July 6, 2023 (https://www.fda.gov/news-events/press-announcements/fda-converts-novel-alzheimers-disease-treatment-traditional-approval).[17] A summary of promising drugs and their approval status by the US FDA is presented in Table 1.

3.2. Challenges in clinical trials

Most of the currently designed drugs for AD target Aβ pathology, aiming to reduce Aβ production, inhibit Aβ plaque formation, promote Aβ plaque clearance, or develop Aβ vaccines.[6,57,59,60] Other drug targets have also been explored for various objectives, including mitigating tau pathology,[61] reducing inflammation,[28] lowering cholesterol accumulation,[62,63] improving brain energy utilization,[64-67] decreasing vascular burden,[68] enhancing neuroprotectant and antioxidant processes,[69-71] increasing neural growth and regeneration,[72,73] and restoring hormonal balance.[74] Among the 2,695 clinical trials for AD (data available at clinicaltrials.gov), when categorized as disease-modifying versus symptomatic, the failure rates are concerning: 41% failed in phase III, while 59% failed in phase II. Of these, 64% were disease-modifying agents, whereas 36% were symptomatic agents.[54]

Several clinical trials have targeted various drug mechanisms, including beta-secretase 1 (BACE1) inhibition, γ-secretase inhibition, γ-Secretase modulation, apolipoprotein E (ApoE) inhibition, Aβ production inhibition, Aβ aggregation inhibition, Aβ dissociation, synaptic modulation, Aβ toxicity modulation, filament modulation, glutaminyl cyclase inhibition, active immunization, passive immunization, receptor for advanced glycation end-products inhibition, and metabotropic glutamate receptor 5 modulation, aiming to reverse or inhibit Aβ pathology or dementia. A summary of the drugs in clinical trials developed for AD treatment is provided in Table 2.

Table 1. List of drugs for Alzheimer's disease treatment with approval status by the United States Food and Drug Administration

Drug name (brand name)	Company	Mode of action and effect	Approval status
Aducanumab (Aduhelm)	Biogen, Neurimmune	Eliminate aggregated Aβ plaques	Approval in progress[17,57,94]
Lecanemab (Leqembi)	BioArctic AB, Biogen, Eisai	Reduce soluble Aβ protofibrils	Fully approved[17,57]
Donanemab (Kisunla)	Eli Lilly and Company	Eliminate aggregated Aβ plaques	Application for full approval[17,57]

Abbreviation: Aβ: Amyloid-beta.

Several potential factors contributed to the failures in clinical trials, whether by faulty drug development processes or the lack of a clear understanding of the complex regulatory mechanisms underlying AD pathology. The main reasons for failures include (i) insufficient evidence to justify clinical trials, (ii) inadequate clinical trial designs, (iii) inappropriate drug designs that fail to align with the rational drug development principles specifically designed for AD therapeutic development,

Table 2. List of drugs developed for Alzheimer's disease treatment

Drug name	Mode of action and effect	Trial phase status	Side effects/outcome
Lenalidomide	BACE1 inhibition, inflammation reduction	Ongoing phase II	Yet to be available[95,96]
CT1812	Aβ aggregation inhibition, Aβ oligomer reduction, behavioral improvement	Ongoing phase II	Yet to be available[97,98]
ALX-001	mGluR5 modulation, synaptic function, and behavioral enhancement	Ongoing phase I	Yet to be available[99,100]
Buntanetap	Aβ production inhibition, Aβ generation reduction	Ongoing phase III	Yet to be available[101,102]
GV-971	Aβ dissociation, Aβ plaque burden reduction	Ongoing phase II	Yet to be available[103,104]
Nasal insulin	Aβ toxicity modulation, memory improvement	Ongoing phase II/III	Yet to be available[105-107]
Simufilam	Disrupts famin A aberrant linkage to the α7 nicotinic acetylcholine receptor (α7nAChR), and blocks soluble amyloid signaling via α7nAChR that hyperphosphorylated tau	Ongoing phase III	Yet to be available[108,109]
Varoglutamstat	Glutaminyl cyclase inhibition, amyloid pathology, and pGlu-Aβ reduction	Ongoing phase II	Yet to be available[110,111]
Aducanumab	Passive immunization, plaque clearance	Approved and ongoing phase III	Application for full approval[17,94]
Lecanemab	Passive immunization, brain, and CSF Aβ protofibril reduction	Approved and ongoing phase III	Approved[17,57]
Donanemab	Passive immunization, plaque clearance	Approved and ongoing phase III	Approved[17,57,112]
Thalidomide	BACE1 inhibition, amyloid pathology, and gliosis reduction	Completed phase III	Adverse consequences[96]
CHF5074	γ-secretase modulation, Aβ reduction	Completed phase II	Decision unavailable[113]
PBT2	RAGE inhibition, spine density, and synaptic protein level improvement	Completed phase II	Lack of efficacy[114]
Contraloid	Aβ aggregation inhibition, amyloid deposition reduction	Completed phase I	Yet to be available[115]
Acitretin	Aβ production inhibition, Aβ reduction	Completed phase II	Yet to be available[116,117]
Bexarotene	Anti-ApoE, Aβ reduction, cognitive deficit improvement	Discontinued phase II	Adverse outcomes/lack of efficacy[118,119]
AN-1792	Active immunization, amyloid plaque formation reduction	Discontinued phase II	Adverse events[120]
ACC-001	Active immunization, amyloid plaque formation prevention	Discontinued phase II	Adverse incidents[121]
CAD106	Active immunization, amyloid accumulation in brain reduction	Discontinued phase II	No results available[122]
Ponezumab	Passive immunization, cerebral blood vessel amyloid deposition reduction	Discontinued phase II	Lack of efficacy[123]
Gammagard	Passive immunization, Aβ reduction	Discontinued phase II	Lack of efficacy[124,125]
Bapineuzumab	Passive immunization, plaque burden reduction	Discontinued phase II	Lack of efficacy[76]
Crenezumab	Passive immunization, localized to Aβ oligomers	Discontinued phase II	Lack of efficacy[126]
Gantenerumab	Passive immunization	Ongoing phase III	Yet to be available[127,128]
Atabecestat	BACE1 inhibition reverses amyloid pathology and cognitive deficit	Discontinued phase II/III	Clinical worsening[76,129]
Elenbecestat	BACE1 inhibition, brain, CSF, and plasma Aβ reduction	Discontinued phase III	Unfavorable risk-benefit ratio[124]
LY2886721	BACE1 inhibition, dose-dependent Aβ reduction	Discontinued phase II	Adverse consequences[122]
Lanabecestat	BACE1 inhibition, Aβ reduction	Discontinued phase III	Lack of efficacy[123]
PF-06751979	BACE1 inhibition, CSF Aβ42 reduction	Discontinued phase I	Pfizer ended R&D in neurology[130,131]
RG7129	BACE1 inhibition, Aβ reduction	Discontinued phase I	Adverse incidents[121,132]
Verubecestat	Dose-dependent Aβ40 and Aβ42 reduction	Discontinued phase III	Clinical worsening[133-135]
Avagacestat	γ-secretase inhibition, CSF Aβ reduction	Discontinued phase II	Clinical worsening/adverse events[127,128]

(Cont'd...)

Table 2. ***(Continued)***

Drug name	Mode of action and effect	Trial phase status	Side effects/outcome
PF-06648671	γ-secretase inhibition, brain Aβ42 reduction	Discontinued phase I	Pfizer ended R&D in neurology[112,136]
Semagacestat	γ-secretase inhibition, soluble Aβ, and plaque reduction	Discontinued phase II	Clinical worsening/adverse events[126]
Azeliragon	γ-secretase modulation, Aβ load reduction, behavioral improvement	Discontinued phase III	Lack of efficacy[137]
Tarenflurbil	γ-secretase modulation, Aβ reduction	Discontinued phase III	Lack of efficacy[94]
Ibuprofen	γ-secretase modulation, Aβ reduction	Discontinued phase II	Lack of efficacy[138]
Clioquinol	Aβ aggregation inhibition, amyloid deposition reduction	Discontinued phase III	Toxic contaminants in manufacturing process[139,140]
ELND005	Aβ aggregation inhibition, amyloid pathology reduction, learning deficit restored	Discontinued phase II	Lack of efficacy[141]
Tramiprosate	Aβ aggregation inhibition, Aβ40 reduction	Discontinued phase III	Lack of efficacy[142,143]

Abbreviations: Aβ: Amyloid-beta; BACE1: Beta-secretase 1; CSF: Cerebrospinal fluid; mGluR5: Metabotropic glutamate receptor 5; pGlu-Aβ: Pyroglutamate Aβ; RAGE: Receptor for advanced glycation end-products; R&D: Research and development.

and (iv) limited therapeutic efficacy.[54] For example, bapineuzumab and solanezumab advanced to phase III trials despite unconvincing phase II results, ultimately leading to failure.[75-77] A critical human error that could have been avoided is the lack of learning from past clinical trials, leading to recurring challenges, negative outcomes, and diminished confidence in AD drug development.[78] Additional factors such as delayed intervention in symptomatic dementia, inappropriate therapeutic targets, and flawed clinical methodologies have further impeded success in AD clinical trials.[79] To overcome these challenges, both clinical and basic research, along with a more intelligent and holistic approach, are crucial in the search for effective treatment of AD and RD.

3.3. Current progress in clinical trials

While most drugs have failed, a few continue to show promising signs and hold hope for success. Three FDA-approved drugs – aducanumab, lecanemab, and donanemab – that target Aβ plaques and protofibrils are still undergoing phase III clinical trials to further examine preventive effects. Comparing the therapeutic effects and data from these trials is expected to help guide future AD drug development. Aducanumab, a human immunoglobulin gamma 1 (IgG1) monoclonal antibody derived from aged donors resistant to AD, binds to the N-terminus of Aβ fibrils but not to Aβ monomers, thereby blocking Aβ aggregation.[80,81] Initially, further clinical trials of aducanumab were terminated due to failure to meet the primary endpoint in Clinical Dementia Rating Scale Sum of Boxes scores.[57] However, two recent phase III clinical trials, the ENGAGE and EMERGE studies, showed significant slowing of cognitive decline at the highest dose. While the EMERGE trial reached statistical significance, the ENGAGE trial did not meet the primary endpoint.[17] Based on these results, the US FDA approved aducanumab, through an "accelerated approval pathway," for the treatment of MCI and mild dementia in AD patients in June 2021, under the brand name Aduhelm by Biogen.[82] Both trials showed intermediate effects on biomarkers, including amyloid removal, which may contribute to the clinical benefit of aducanumab. The phase phase IIIb/IV ENVISION trial (ClinicalTrials.gov ID: NCT05310071) is currently ongoing.[17,57]

Donanemab is another humanized IgG1 monoclonal antibody developed from mouse mE8-IgG2a, which targets the Aβ (3 – 42), a pyroglutamate form of Aβ, that is abundant in the brains of AD patients.[83,84] Interestingly, donanemab can bind to approximately one-third of Aβ plaques in post-mortem AD and Down syndrome brains, strongly reacting with plaque cores.[85] In the phase II TRAILBLAZER-ALZ study (https://clinicaltrials.gov/study/NCT04437511), combination therapy using donanemab and BACE1 inhibitor LY3202626 was administered to target the pyroglutamate form of Aβ. The treatment met the primary endpoint of delaying cognitive decline as assessed by the Integrated AD Rating Scale.[17,57] Reduction of Aβ burden was correlated with improvement in the scores but only in APOE4 carriers.[86] Donanemab also reduced tau aggregation in the temporal, parietal, and frontal lobes and significantly lowered plasma pTau217 levels.[87] Phase I clinical trials of donanemab demonstrated sustained reduction in cortical amyloid load, with the treatment being well tolerated.[88] While phase II trials of donanemab replicated phase I results with no adverse effects, patients were more likely to exhibit amyloid-related imaging abnormalities amyloid-related imaging abnormalities with vasogenic

edema, and amyloid-related imaging abnormalities with microhemorrhages.[89] Phase III clinical trials for donanemab are currently ongoing.

On the other hand, LY3202626 and most BACE1 inhibitors were excluded from further trials due to insufficient evidence of safety and efficacy, except lenalidomide.[57] The US FDA granted traditional approval for lecanemab under the brand name Leqembi, in July 2023 for the treatment of AD.[90] Lecanemab, a humanized IgG1 antibody derived from mAb158, selectively binds to soluble Aβ protofibrils.[91,92] In phase II clinical trials involving AD patients with MCI or mild dementia, confirmed by amyloid pathology through amyloid positron emission tomography scan or CSF Aβ(1-42) levels, the results showed a significant dose-dependent reduction in Aβ plaque.[91] Positive outcomes were observed across all primary and secondary measures, including the AD Assessment Scale–Cognitive Subscale, AD Composite Score, and AD Cooperative Study-MCI-Activities of Daily Living Inventory scores.[93] The phase III clinical trial for lecanemab is currently ongoing. These findings suggest that while a definitive drug or treatment for dementia related to AD and RD remains unavailable, there is still hope for progress in the field.

4. Discussion

The regulatory mechanisms underlying the pathology of dementia in AD and RD are highly complex, and no effective treatment is currently available. A more detailed investigation is needed to uncover unknown pathways that could facilitate drug design for the treatment of cognitive impairments caused by AD and RD. Despite significant efforts and extensive studies aimed at understanding disease pathology and finding a cure, no breakthrough therapy has been established. However, research has greatly expanded our knowledge of the regulatory mechanisms involved, identifying multiple potential pathways that contribute to mild, moderate, or severe cognitive deficits in AD and RD. Although several drugs have been developed to target cognitive impairment, the challenges remain profound due to the intricate regulatory pathways of these diseases. In addition to gaps in understanding disease pathology, the design and methodology of clinical trials have been critically examined and debated as contributing factors to drug development failures. Three promising drugs – aducanumab, lecanemab, and donanemab – are still undergoing phase III clinical trials to assess their preventive effects. While lecanemab has received US FDA approval, aducanumab and donanemab are still in the process of regulatory review. Comparing the therapeutic effects across these trials is expected to guide future AD drug development.

Although most drug candidates have failed to demonstrate efficacy, the positive outcomes of a few drugs keep the hope of success alive. Current clinical trials primarily focus on disease-modifying therapies. To enable preventive interventions before irreversible brain damage occurs, early-stage participant recruitment is crucial. This highlights the importance of fundamental research on AD pathology in its early stages. Most drug designs have focused on inhibiting toxic Aβ and pTau aggregation. However, expanding research has introduced new therapeutic possibilities, including the promising outcomes of aducanumab, lecanemab, and donanemab, which successfully clear Aβ plaques and protofibrils. A vast number of studies have demonstrated that modulating chronic neuroinflammation, regulating microglial phagocytosis, and promoting myelination improve Aβ clearance. These findings suggest that passive immunotherapy targeting neuroinflammatory responses holds significant therapeutic potential. Moreover, early detection of AD could allow for timely therapeutic intervention.

Other monoclonal antibody drugs currently in phase III trials are remternetug (ClinicalTrials.gov identifier: NCT05463731) and solanezumab (ClinicalTrials.gov identifier: NCT01760005). Inflammatory pathways involving inflammasomes that are associated with potential AD biomarkers, such as nuclear factor kappa B, NLR family pyrin domain-containing 3, and triggering receptor expressed on myeloid cells 2, have emerged as potential drug targets for AD.[144] Given that multiple pathways contribute to neurodegeneration, leading to cognitive deficits in AD and RD, single-target drug approaches have proven insufficient. A more effective strategy would involve the simultaneous application of multiple drugs targeting different regulatory pathways.

Research has also revealed common disease pathways among neurodegenerative diseases,[145] suggesting that the findings from AD studies may be applicable to other dementias. Understanding the histopathologic changes underlying neurodegenerative diseases is crucial for advancing AD and RD research and developing effective treatment, as it can reveal key mechanisms of neurodegeneration that contribute to dementia. Furthermore, the persistent failures in AD clinical trials necessitate a thorough reassessment of drug design strategies and clinical trials methodologies. Moving forward, both basic and clinical research must be expanded, integrating diverse approaches to unravel the complex causes of AD and RD and develop more effective treatments.

5. Conclusion

AD and RD are complex neurodegenerative diseases that severely affect the lives of millions globally, with mortality

rates continuing to increase over the years. Moreover, individuals with dementia require lifelong caregiving. These diseases demand urgent attention to develop effective preventive and curative treatments. Through in-depth research, innovative drug design, and systematic clinical trials, the discovery of effective treatments for AD and RD may become a reality in the near future.

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REVIEW ARTICLE

The role of open-source bioinformatics tools in resource-limited African settings

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Abstract

Bioinformatics is revolutionizing biological research and healthcare worldwide, yet many African countries face significant challenges due to limited access to registered tools and infrastructure. Despite these challenges, open-source bioinformatics tools provide a cost-effective alternative, driving scientific progress. This systematic review examines their impact and applications in resource-limited African settings, particularly in genomics, drug discovery, disease surveillance, and structural biology. A comprehensive literature search of PubMed, Google Scholar, and African Journals Online was conducted using keywords such as "open-source bioinformatics," "Africa," and "genomics," covering studies from 2015 to 2024. The findings highlight significant contributions across multiple fields. In genomics, studies on sickle cell anemia in Nigeria identified novel single nucleotide polymorphisms using FastQC and Burrow–Wheeler alignment, improving genetic counseling and personalized treatments. Crop genomics research in Kenya pinpointed drought-resistance genes, enhancing food security. In disease surveillance, Nextstrain facilitated real-time tracking of viral mutations during the Ebola and COVID-19 outbreaks, shaping public health responses and vaccination strategies. In drug discovery, computational docking with AutoDock identified promising antimalarial and multidrug-resistant tuberculosis drug candidates in Uganda and South Africa, wherease molecular dynamics simulation and binding free energy analysis refined drug-target interactions. Structural biology contributions from African researchers to the Protein Data Bank have provided crucial insights for disease-specific treatments, such as targeting malaria-related proteins. In addition, absorption, distribution, metabolism, excretion, and toxicity predictive models have been employed to assess the pharmacokinetics and toxicity profiles of novel drug candidates, reducing reliance on costly experimental studies. These findings underscore the transformative potential of open-source bioinformatics tools in enabling high-quality research and innovation in Africa.

Keywords: Bioinformatics; Open-source tools; Genomics; Resource-limited settings; African research; Computational biology; Disease surveillance

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1. Introduction

Bioinformatics is often described as an interdisciplinary field comprising biology, computer science, and mathematics. It has developed biological research, healthcare, and agriculture. In well-developed countries, proprietary bioinformatics tools are

widely used to analyze complex biological data, driving innovation and scientific discovery. However, in many African nations, the high costs of proprietary software licenses, inadequate infrastructure, and limited access to training pose significant barriers.[1-3] These challenges hinder the continent's ability to keep pace with global advancements, limiting its potential to contribute to scientific breakthroughs that could address pressing local and global issues.[4-7]

The disparity in access to bioinformatics tools is particularly pronounced in Africa, where researchers face unique challenges such as disease outbreaks, food insecurity, and underdeveloped healthcare systems. Despite the transformative potential of bioinformatics in addressing these issues, the reliance on expensive proprietary software has left many African scientists unable to leverage these technologies fully.[8-10] For example, the lack of computational infrastructure and reliable internet connectivity has been a major bottleneck for large-scale genomic studies and data analysis.[11-13] In addition, the shortage of skilled bioinformaticians, stemming from limited training opportunities, has further exacerbated the problem.[14,15] This gap has created an urgent need for affordable and accessible alternatives to empower researchers to conduct more advanced research without the financial and infrastructural burdens associated with proprietary tools.[14,16,17]

Open-source bioinformatics tools have emerged as a viable resolution to these challenges. By providing free access to powerful computational resources, these tools allow extensive research and foster a collaborative environment that surpasses geographical and financial barriers.[18-21] Open-source platforms, which include Bioconductor, Galaxy, R, and Python libraries (e.g., Biopython), have enabled African researchers to perform sophisticated bioinformatics tasks. Some of these include genomic sequencing to drug discovery, without the need for costly trademarked software.[17,22,23] These tools have demonstrated their potential in addressing critical issues such as infectious disease outbreaks, agricultural productivity, and healthcare delivery across the continent.[24-26]

For instance, during the COVID-19 pandemic, open-source tools such as Nextstrain and Galaxy played a pivotal role in tracking SARS-CoV-2 variants and mapping the spread of the virus in real-time.[27,28] Similarly, in agricultural research, open-source platforms have supported crop genome sequencing, enabling the development of drought-resistant varieties to combat food insecurity.[9,29] In drug discovery, tools such as AutoDock and PyMOL have facilitated virtual screenings and molecular docking studies, accelerating the identification of potential treatments for diseases such as malaria and tuberculosis (TB).[30-32]

Despite these successes, significant challenges remain. Infrastructure limitations, such as unreliable electricity and inadequate internet connectivity, continue to hinder the widespread adoption of bioinformatics tools in many parts of sub-Saharan Africa.[11,12] In addition, the shortage of trained bioinformaticians and the lack of formal education programs pose ongoing barriers to capacity building.[14,15] Furthermore, issues related to data ownership and the reliance on international collaborators with more advanced infrastructure have raised concerns about the equitable sharing of research outputs.[33,34]

This paper explores the transformative role of open-source bioinformatics tools in overcoming the unique challenges faced by African researchers. It highlights their practical applications in genomics, drug discovery, disease surveillance, and structural biology, while also addressing the infrastructural and training gaps that persist.[23,35,36] By showcasing real-world examples and success stories, this study aims to underscore the importance of open-source tools in advancing scientific research and innovation in a resource-limited setting.[26,36,37] Furthermore, it seeks to provide a comprehensive understanding of how these tools can bridge the gap between need and accessibility, ultimately contributing to developing sustainable solutions for Africa's most pressing challenges.[20,37]

1.1. Research objectives

This paper aims to:

(i) Highlight the practical use of open-source bioinformatics tools in African settings where resources are scarce
(ii) Demonstrate how these tools help overcome barriers, such as financial constraints and infrastructural challenges
(iii) Explore the impact of open-source bioinformatics tools on research, healthcare, and agriculture in Africa.

1.2. The need for bioinformatics in Africa

Africa faces numerous health-related challenges, including frequent disease outbreaks, food insecurity, and under-resourced healthcare systems. Bioinformatics holds the potential to address these issues, advancing research in genomics, drug discovery, and agriculture. However, access to high-cost proprietary tools remains out of reach for many researchers. Open-source bioinformatics tools have emerged as critical resources, bridging the gap between need and accessibility.

1.3. Overview of open-source bioinformatics tools

Tools such as Bioconductor, Galaxy, R, and Python libraries (e.g., Biopython) provide accessible, robust functionalities for data analysis, molecular docking, and genomic sequencing. By reducing financial barriers, they democratize research, allowing African scientists to perform sophisticated bioinformatics tasks without relying on expensive proprietary software. Many platforms also support collaborative cloud-based research, addressing infrastructural challenges faced by African institutions.[38]

1.4. Applications in genomics and healthcare

Several real-world examples highlight the transformative potential of open-source tools in Africa:

(i) Genomic studies: Platforms have supported crop genome sequencing, facilitating the development of drought-resistant varieties. This is vital for improving food security in the face of climate change[39]

(ii) Infectious disease research: During outbreaks such as Ebola and COVID-19, tools such as Galaxy and Nextstrain helped analyze viral genomes, track mutations, and model epidemics in real-time, shaping public health responses

(iii) Drug discovery: Open-source platforms such as AutoDock and PyMOL have enabled researchers to conduct virtual screenings and assess potential drug treatments for diseases such asmalaria and TB. These tools speed up the discovery process, reducing reliance on costly proprietary software.

1.5. Challenges and opportunities

Despite the benefits, several challenges remain. These include:

(i) Infrastructure limitations: Reliable electricity, fast internet, and powerful computing resources are still lacking in many parts of Sub-Saharan Africa, preventing large-scale bioinformatics projects

(ii) Training needs: The shortage of skilled bioinformaticians is another challenge, stemming from a lack of formal education programs. Initiatives such asthe Pan African Bioinformatics Network for the Human Heredity and Health in Africa aim to bridge this gap by offering specialized training and building local capacity[14]

(iii) Data ownership: African researchers often face challenges maintaining control over their data, due to reliance on international collaborators with more advanced infrastructure.

The literature highlights the transformative role of open-source bioinformatics tools in resource-limited settings. These tools are essential for addressing specific African challenges in healthcare, agriculture, and disease research. However, more documentation of practical applications is needed. This study aims to fill that gap by showcasing concrete examples and success stories across the continent.

2. Methodology

2.1. Data collection

The literature search followed a structured workflow (Figure 1), beginning with systematically retrieving peer-reviewed articles from PubMed, Google Scholar, and African Journals Online, alongside institutional reports and Protein Data Bank (PDB) data. For institutional reports, reports from African research centers and bioinformatics initiatives were reviewed. PDB was used to identify relevant protein structures, especially those related to African diseases.

The inclusion criteria of the review included studies from African countries, studies using open-source

Figure 1. Flow diagram of the methodology. Image created using open-source logos and images.

bioinformatics tools, and studies encompassing the fields of genomics, drug discovery, and disease surveillance.

2.2. Data categorization

Data was organized into three key categories: (i) genomics (human and agricultural genomic studies), (ii) infectious disease research (viral genome analysis), and (iii) drug discovery (molecular docking studies), as visualized in Figure 2, with supplementary integration of PDB structures. The findings were correlated with PDB data where applicable, ensuring protein structures relevant to African studies are included in the analysis.

2.3. Data analysis

Thematic analysis (Figure 3) revealed critical insights (success stories), including infrastructure challenges, training needs, and the role of structural biology tools in African research contexts. Following the thematic analysis, PDB data were linked to the thematic categories (e.g., how structural biology tools support disease research or agricultural advancements) for a more comprehensive insight.

2.4. Case study selection

Representative examples were chosen from impactful case studies illustrating the use of open-source tools and PDB contributions in real-world African contexts. For validation, the findings were cross-checked with multiple sources to ensure they were accurate and relevant.

3. Results

3.1. Genomics applications

3.1.1. Human genomics

An extensive genomic analysis was conducted focusing on Nigerian populations to uncover genetic variations linked to sickle cell anemia.[40] Using bioinformatics tools such as FastQC for quality control and Burrow–Wheeler Aligner

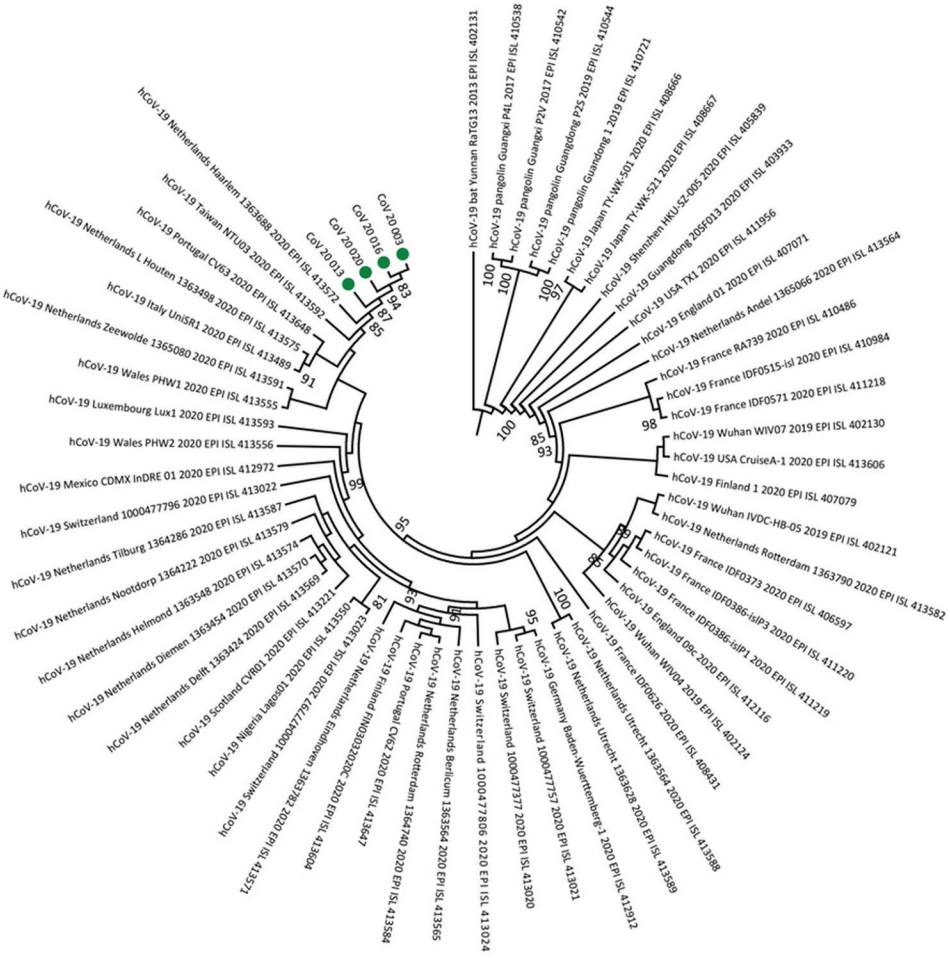

Figure 2. Phylogeny of four severe acute respiratory syndrome coronavirus 2 strains isolated from Senegal. Reproduced from Dia *et al.*[59]

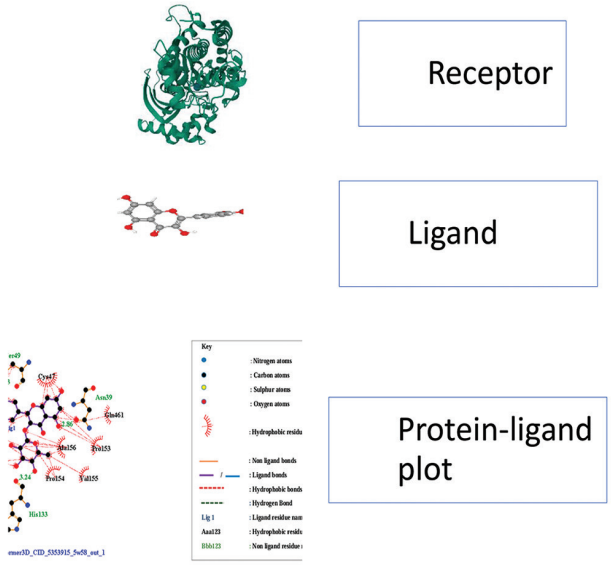

Figure 3. A pictorial summary of molecular docking. The figure depicts the methodological approach used by scientists to analyze the bonds involved.

(BWA) for aligning sequencing reads, the study identified specific single nucleotide polymorphisms within the *HBB* gene influencing hemoglobin structure and disease severity. These findings have improved genetic counseling services and enabled the development of personalized treatment strategies, such as targeted hydroxyurea therapy and improved blood transfusion protocols in high-prevalence regions.[41]

3.1.2. Crop improvement (Genomic selection)

The case study included was on drought-resistant maize in Kenya. It was reported that the authors utilized bioinformatics platforms such as Bioconductor and Galaxy to analyze the genomes of drought-tolerant maize strains. The study identified key genes, such as *ZmDREB2A* and *ZmNAC111*, that regulate the plant's response to water stress. These genes have been integrated into marker-assisted breeding programs, resulting in the development of maize varieties that thrive in drought-prone environments, thereby enhancing food security in Kenya's semi-arid regions.[42]

3.2. Infectious disease research

3.2.1. Ebola virus surveillance (West Africa)

During the devastating 2014 – 2016 Ebola outbreak in West Africa, tools like Nextstrain played a critical role in real-time viral surveillance.[43] By sequencing genomes from infected individuals, researchers could meticulously track the virus's evolution and transmission patterns. Real-time evolution tracking using Nextstrain enabled researchers to monitor viral mutations in real-time, revealing the virus's adaptive capabilities and the emergence of potentially more virulent strains.[44,45] Genetic analyses helped map out transmission routes, enabling authorities to trace the origins and progression of outbreaks accurately. In addition, insights from genomic data directly influenced public health responses, optimizing contact tracing, isolation, and quarantine protocols.[46]

A mutation in the glycoprotein gene *GP-A82V* emerged as particularly concerning due to its association with increased transmissibility. This discovery helped prioritize containment efforts in high-risk regions and shaped targeted interventions.

3.2.2. COVID-19 genomic surveillance (South Africa)

South Africa's robust genomic surveillance, powered by platforms like Global Initiative on Sharing All Influenza Data (GISAID) and Nextstrain, has been pivotal in monitoring the evolution and spread of SARS-CoV-2. Sequencing viral genomes from local cases enabled the early detection of variants of concern, such as the Beta variant B.1.351.[47]

Genomic surveillance has been a game changer, particularly with the early detection of the Beta variant. This variant, characterized by increased transmissibility and immune evasion, posed a serious challenge. Its early identification through advanced sequencing technologies allowed South African health authorities to take action quickly.[48]

The discovery of the Beta variant was not just a scientific achievement; it had real-world consequences. Prompt identification led to targeted lockdowns and accelerated vaccination campaigns. These data-driven interventions helped mitigate a potentially catastrophic surge. It shows how science directly influences policy and saves lives.[47]

Genomic data also paved the way for better vaccine strategies. Understanding the Beta variant's impact on vaccine efficacy guided developers to tweak existing formulations. Proactive detection and response helped safeguard populations by tailoring interventions. Without this foresight, the situation could have been chaotic.[47]

For example, early detection of the Beta variant led to rapid development and deployment of vaccines designed to target its structure. This proactive approach reduced the variant's impact on South Africa's population. It may not have been perfect, but it was effective and protected lives.

3.3. Phylogenetic analysis in disease tracking

3.3.1. Phylogenetic tree construction for Ebola

In 2014, an Ebola outbreak occurred across West Africa. Gire *et al.*[43] used Bayesian evolutionary analysis sampling

trees to construct detailed phylogenetic maps of the outbreak. The insights went beyond revealing transmission dynamics; they pinpointed mutation clusters within Sierra Leone and Guinea. One major discovery was a transmission cluster linked to a single funeral event. This finding underscored the need for community-focused containment strategies, which are often overlooked in the rush to control an outbreak. Similar phylogenetic approaches, like those applied to SARS-CoV-2 strains from Senegal (Figure 2), demonstrate how open-access genomic data and tools can clarify transmission patterns and inform public health decisions.

3.3.2. Tracking malaria parasite evolution

Malaria remains a formidable adversary, especially with rising drug resistance. Ndounga *et al.*[49] mapped genetic variations in *Plasmodium falciparum* and identified mutations linked to artemisinin resistance. Using tools such as randomized accelerated maximum likelihood (RAxML) and molecular evolutionary genetics analysis, they pinpointed critical mutations in the K13-propeller domain. These markers are now central to treatment protocols in malaria-endemic regions such as Kenya and Nigeria. Without this genetic research, we would be proceeding without crucial insights.

3.4. Drug discovery applications

3.4.1. Molecular dynamics (MD) simulation in African research

MD simulations, facilitated by tools such as GROMACS and Nanoscale MD (NAMD), have provided critical insights into the dynamic behavior of drug targets and their interactions with potential therapeutics. In Africa, MD simulations have had a particularly significant impact on the following areas: malaria research and TB drug discovery.

For malaria research, researchers in Uganda and Nigeria have used MD simulations to study the PfATP6 protein, a key drug target in *P. falciparum*, the parasite responsible for malaria. By simulating the protein's conformational changes, researchers identified binding sites for artemisinin-based compounds, leading to the development of more effective antimalarial drugs. For example, a study in Uganda used MD simulations to optimize the binding of a traditional medicinal compound derived from *Artemisia annua*, resulting in a potential new antimalarial drug candidate.[50]

Furthermore, MD simulations have been employed in South Africa to study the *Mycobacterium tuberculosis* DNA gyrase enzyme, a target for TB drugs. Researchers used GROMACS to simulate the binding of rifapentine derivatives to the enzyme, identifying compounds with improved binding affinity and reduced resistance. This approach has accelerated the development of new TB therapies, particularly for multidrug-resistant TB, which is a major public health challenge in the region.[51]

3.4.2. Binding free energy analysis

Binding free energy calculations, using methods such as molecular mechanics/Poisson–Boltzmann surface area, have enhanced the accuracy of drug-target interaction predictions. In Africa, these analyses have been applied to human immunodeficiency virus (HIV) drug development and antimalarial drug optimization.

For HIV drug development, researchers in Kenya[52] used binding free energy analysis to evaluate the interactions between HIV protease inhibitors and their target proteins. By quantifying the binding strengths of various compounds, they identified promising candidates for further experimental testing.[52] This approach has reduced the time and cost of traditional drug screening methods, making it particularly valuable in resource-limited settings.

For antimalarial drug optimization, researchers in Ghana[53] used binding free energy analysis to optimize the binding of dihydroartemisinin derivatives to the PfATP6 protein. The results guided the synthesis of new compounds with improved efficacy and reduced toxicity, addressing the challenge of artemisinin resistance in malaria-endemic regions.[53]

3.4.3. Absorption, distribution, metabolism, excretion, and toxicity (ADMET) analysis in African contexts

ADMET analysis is critical in drug discovery, ensuring that potential drug candidates have favorable pharmacokinetic and safety profiles. Open-source tools like ADMET lab have been widely adopted in Africa for various applications.

Researchers in Tanzania[54] used ADMET analysis to screen a library of natural compounds derived from local medicinal plants. By predicting the ADMET properties of these compounds, they identified several candidates with potential antimalarial and anti-TB activity. This approach combines traditional knowledge with modern computational methods, providing a cost-effective strategy for drug discovery.[54]

In Nigeria, ADMET analysis was used to evaluate the safety and efficacy of potential drugs for sickle cell anemia. By predicting the toxicity profiles of hydroxyurea derivatives, researchers identified safer alternatives for long-term use, improving treatment options for patients in high-prevalence regions.[55]

3.4.4. Population linkage or pedigree linkage

In addition to FastQC and BWA, tools like PLINK have been instrumental in analyzing large-scale genomic datasets, enabling researchers to identify genetic variants associated with complex diseases. It is a widely used open-source toolset for genome-wide association studies and genetic data analysis.[56] For example, PLINK has been used in studies on HIV resistance in South Africa, providing insights into host-pathogen interactions.

3.4.5. Multiple alignment using fast Fourier transform (MAFFT)

MAFFT is an open-source bioinformatics tool used for multiple sequence alignment, which is essential for comparing and analyzing DNA, RNA, or protein sequences. MAFFT is known for its speed, accuracy, and ability to handle large datasets, making it a popular choice for phylogenetic analysis, evolutionary studies, and functional annotation.

Key features of MAFFT include high accuracy, as it uses advanced algorithms (e.g., fast Fourier transform) to align sequences with high precision, high speed (optimized for rapid alignment of large datasets, even with thousands of sequences), and flexibility, as it supports various alignment strategies, including progressive, iterative, and consistency-based methods. It is also user-friendly, offering both command-line and web-based interfaces for ease of use. It is compatible with other bioinformatics tools for downstream analysis, such as phylogenetic tree construction. MAFFT has been instrumental in advancing genomic and infectious disease research in Africa.

Under HIV and Ebola research, MAFFT has been used to align viral genomes from the HIV and Ebola outbreaks in Africa. For example, during the 2014 – 2016 Ebola outbreak in West Africa, researchers used MAFFT to align viral sequences from different patients.[43] This allowed them to track the evolution of the virus, identify key mutations associated with increased transmissibility or virulence, and inform public health strategies, such as targeted containment and vaccine development.

Moreover, MAFFT has been used to align sequences of the *P. falciparum* parasite, which causes malaria. By comparing sequences from different regions of Africa, researchers have identified genetic variations linked to drug resistance.[57] This has helped develop region-specific treatment protocols and prevent the spread of drug-resistant malaria strains.

For genomic studies, MAFFT has been employed in various fields, such as crop and human genomics. In the context of crop genomics, MAFFT was used in agricultural research to align sequences of drought-resistant crops, such as maize and sorghum. For example, in Kenya, researchers used MAFFT to compare the genomes of drought-tolerant and drought-susceptible maize varieties.[42] This led to the identification of key genes (e.g., *ZmDREB2A*) involved in drought resistance, the development of improved crop varieties through marker-assisted breeding, and the enhancement of food security in drought-prone regions.

In addition, MAFFT has been used to study genetic diseases prevalent in Africa, such as sickle cell anemia. By aligning sequences of the *HBB* gene from different populations, researchers have identified novel single nucleotide polymorphisms associated with disease severity and population-specific genetic markers for personalized medicine.

Besides infectious disease research and genomic studies, MAFFT has also been used in phylogenetic analysis. MAFFT has been used to construct phylogenetic trees for pathogens like *M. tuberculosis* (the causative agent of TB) and SARS-CoV-2 (responsible for COVID-19). For example, during the COVID-19 pandemic, researchers in South Africa used MAFFT to align viral genomes and track the emergence of the Beta variant (B.1.351).[58] This enabled early detection of the variant, rapid public health responses, including lockdowns and vaccine deployment, and global sharing of genomic data through platforms like GISAID.

In summary, these tools have fostered local expertise in computational drug discovery, empowering African researchers to develop homegrown solutions to regional health problems.

3.5. Structural biology insights: PDB

3.5.1. African contributions to structural biology

African researchers have made significant contributions on the global scientific stage. A notable example is the deposition of the *P. falciparum* dihydrofolate reductase (PfDHFR) structure into the PDB. Molefe *et al.*[60] showed that inhibitors binding to PfDHFR could significantly reduce its activity, which is critical for next-gen antimalarial drugs.[60] This demonstrates the region's growing scientific prowess.

3.5.2. PDB data for African-specific diseases

The PDB, combined with tools such asBioPython and PyMOL, has transformed our understanding of pathogen structures. Structural analyses of the *M. tuberculosis* KasA protein revealed novel binding sites for potential inhibitors. This work goes beyond academic curiosity; it is vital for developing treatments tailored to Africa's needs.

Structural biology is not merely a theoretical pursuit; it is an essential tool in the fight against disease. As illustrated in Figure 3, molecular docking workflows are more than academic exercises; they represent a critical pathway toward developing treatments tailored to Africa's disease burden.

3.6. Bioinformatics applications and findings in resource-limited African settings

Table 1 summarizes the transformative role of open-source bioinformatics tools in addressing Africa's healthcare and agricultural challenges, emphasizing cost-effectiveness and regional collaboration.

4. Discussion

Adopting open-source bioinformatics tools in Africa has demonstrated significant potential in addressing health challenges and enhancing research capabilities in resource-limited settings. Unlike proprietary software, which often carries high licensing fees and limited accessibility, open-source tools such as Bioconductor, Nextstrain, AutoDock, FastQC, BWA, GROMACS, NAMD, PLINK, and MAFFT offer cost-effective and scalable solutions for African researchers. These tools have been crucial in genomics research, disease tracking, drug discovery, and MD simulations, allowing local scientists to conduct high-quality research without financial strain.[61,62]

For instance, during the Ebola and COVID-19 outbreaks, Nextstrain played a pivotal role in the real-time tracking of viral mutations, which was critical for informing public health responses. Similarly, AutoDock has facilitated the identification of potential drug candidates for malaria and TB by integrating computational approaches with traditional medicinal knowledge. Similarly, GISAID has enabled African researchers to contribute to global pathogen surveillance, significantly enhancing pandemic preparedness and response.[61] These examples highlight how open-source bioinformatics tools empower researchers to generate data that informs public health strategies, accelerate drug development, and uncover disease mechanisms specific to African populations.[63]

MD simulations, facilitated by tools like GROMACS and NAMD, have provided critical insights into the dynamic behavior of drug targets and their interactions

Table 1. Summary of bioinformatics tools and applications

Category	Application area	Scientific achievement	Tools used	Impact/outcome
Genomics	Human genomics	Identification of novel single nucleotide polymorphisms linked to sickle cell anemia.	FastQC, Burrow–Wheeler Aligner	Improved early diagnosis and tailored therapies for sickle cell anemia.
	Crop improvement	Identified drought-tolerance genes (e.g., *ZmDREB2A, ZmNAC111*) in maize.	Bioconductor, Galaxy	Accelerated marker-assisted breeding, enhancing drought resistance.
Infectious disease research	Ebola surveillance	Real-time tracking of viral mutations during the 2014 – 2016 outbreak.	Nextstrain	Optimized public health responses, including targeted containment efforts.
	Covid-19 surveillance	Early detection of the Beta variant (B.1.351).	Global Initiative on Sharing All Influenza Data, Nextstrain	Informed lockdowns, vaccination strategies, and mitigated variant impact.
Phylogenetic analysis	Ebola outbreak	Identified transmission clusters and mutation hotspots.	Bayesian evolutionary analysis sampling trees	Highlighted the importance of community-focused containment strategies.
	Malaria evolution	Detected artemisinin-resistance mutations in *Plasmodium falciparum*.	Randomized accelerated maximum likelihood, molecular evolutionary genetics analysis	Enhanced treatment protocols to combat drug resistance.
Drug discovery	Malaria research	Identified potential antimalarial compounds targeting the PfATP6 protein.	AutoDock	Promoted affordable treatments combining computational and traditional medicine.
	Tuberculosis research	Discovered rifapentine derivatives targeting *Mycobacterium tuberculosis* DNA gyrase.	AutoDock	Suggested new therapeutic strategies for multidrug-resistant tuberculosis.
Structural biology	Protein Data Bank contributions	Analysis of *Plasmodium falciparum* dihydrofolate reductase inhibitors, aiding next-generation antimalarial drugs.	Protein Data Bank, PyMOL	Highlighted African research contributions and potential for disease-specific treatments.

with potential therapeutics. MD simulations have had a particularly impactful impact on malaria and TB research in Africa. Researchers in Uganda and Nigeria have used MD simulations to study the PfATP6 protein, a key drug target in *Plasmodium falciparum*, leading to the development of more effective antimalarial drugs.[64] Similarly, MD simulations have been employed in South Africa to study the *M. tuberculosis* DNA gyrase enzyme, a target for TB drugs, identifying compounds with improved binding affinity and reduced resistance.[65]

Binding free energy calculations using methods such as molecular mechanics/Poisson–Boltzmann surface area have enhanced the accuracy of drug-target interaction predictions. In Kenya, binding free energy analysis has been used to evaluate HIV protease inhibitors, reducing the time and cost associated with traditional drug screening methods.[66] Similarly, in Ghana, this approach has optimized the binding of dihydroartemisinin derivatives to the PfATP6 protein, addressing the challenge of artemisinin resistance in malaria-endemic regions.[53]

Another key computational approach is ADMET analysis, which ensures that potential drug candidates have favorable pharmacokinetic and safety profiles. Open-source tools like ADMETlab have been widely adopted in Africa for research on malaria, TB, and sickle cell anemia. ADMET analysis has been used in Tanzania to screen natural compounds derived from local medicinal plants, identifying potential antimalarial and anti-TB agents.[54] Similarly, in Nigeria, ADMET analysis has helped evaluate the safety and efficacy of hydroxyurea derivatives for sickle cell anemia treatment.[40]

Genomic research in Africa has also benefited from tools such as PLINK and MAFFT. PLINK has been instrumental in genome-wide association studies and genetic data analysis, helping researchers in South Africa identify genetic variants associated with HIV resistance.[56] MAFFT, a powerful tool for multiple sequence alignment, has been widely used in infectious disease research, crop genomics, and human genetics. For example, during the Ebola outbreak in West Africa, MAFFT was used to align viral sequences and track key mutations affecting transmissibility and virulence.[43] In malaria research, MAFFT has facilitated the study of genetic variations linked to drug resistance, aiding in developing region-specific treatment protocols.[49] In addition, MAFFT has been used in crop genomics to identify drought-resistant genes in maize and sorghum, contributing to agricultural resilience in drought-prone regions.[42]

A key advantage of open-source tools is their affordability, which is transformative for African countries with limited research funding.[67] By eliminating the high costs associated with proprietary software, researchers can access cutting-edge technology and conduct sophisticated analyses without financial barriers.[68] This democratization of scientific tools enables greater participation in global research efforts and fosters innovation within the continent.

However, despite these advantages, several challenges hinder the widespread adoption of open-source bioinformatics tools in Africa. Limited internet access, scarce computational resources, and inadequate local training programs present significant obstacles.[62] Proprietary tools often come with dedicated support and user-friendly interfaces, which open-source alternatives may lack. In addition, interoperability between different bioinformatics platforms remains a challenge. For example, tools such as PhyML and RAxML could provide greater insights if integrated seamlessly with disease-specific applications.[68] Overcoming these limitations will require concerted efforts to enhance the usability and compatibility of open-source tools.

On a positive note, advancements in satellite internet, such as Starlink, are reshaping the digital landscape by providing reliable connectivity to remote areas. This development allows researchers in rural regions to access critical bioinformatics tools and participate in global research networks, thus bridging the digital divide.[69] Expanding digital infrastructure will ensure equitable access to bioinformatics resources across Africa.

Another pressing issue is the scarcity of African-specific genomic data. While databases such as the PDB include structures from African pathogens, more contributions are needed, particularly for underrepresented diseases.[70] Increasing African participation in global databases will significantly improve the quality and relevance of research conducted on the continent. Addressing this gap requires strategic data collection and curation investments to build comprehensive genomic datasets tailored to local health challenges.[67]

The continued development and adoption of open-source bioinformatics tools and investments in digital infrastructure and training will be crucial for sustaining their impact in Africa. Initiatives that provide access to open-source software, hardware, and internet resources for low-resource institutions will amplify the benefits of bioinformatics.[68] Collaborative networks, such as the African Bioinformatics Network, can play a pivotal role in fostering knowledge exchange and driving joint research efforts.[70]

African researchers are uniquely positioned to tackle region-specific health challenges. By leveraging open-source bioinformatics tools, they can identify biomarkers

for diseases such as malaria and TB, leading to improved diagnostics and targeted treatments.[61] Strengthening bioinformatics training and encouraging collaboration with international partners will be key to building local expertise and ensuring long-term success. With the right resources, African researchers can significantly contribute to global science while addressing pressing local health issues.[67]

5. Conclusion

Open-source bioinformatics tools are game-changers for genomics research and healthcare across Africa, especially in regions with limited resources. Tools such as GISAID, Nextstrain, and Bioconductor empower local scientists to address urgent health issues, track infectious diseases, and explore drug discovery without purchasing proprietary software. For researchers on the front lines, these tools are useful and essential. The response to outbreaks such as Ebola and COVID-19 has shown how transformative open-source platforms can be, boosting local capacity and innovation.

However, challenges persist. Infrastructure, reliable internet access, and computational power can be scarce. These challenges are not just technical issues, but the reality limiting progress. However, there is potential for improvement through Starlink's rollout in various African countries. With improved connectivity, even in remote areas, researchers can access bioinformatics tools more easily and foster better international collaboration. This advancement is beyond the context of internet access; it is about breaking down barriers literally and figuratively to foster new ideas and innovation.

However, there is another big challenge: data. African-specific data is still underrepresented in global databases, such as the PDB. It offers invaluable protein structure information, but the continent's contributions remain limited. It is crucial to have more African representation in these databases, with research that truly reflects and addresses Africa's unique health challenges.

In conclusion, open-source bioinformatics holds immense potential for Africa. However, realizing that potential will require tackling infrastructure gaps, investing in local training, and encouraging contributions to global databases. With continued support and better access to these tools, the future of bioinformatics in Africa is hopeful and promising. This could lead to potential breakthroughs emerging locally to address some of the continent's most pressing health issues.

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ACCSCIENCE PUBLISHING

Innovative Medicines & Omics

REVIEW ARTICLE

The accessibility and usage patterns of herbal drug information among non-health professionals in Nigeria: A narrative review

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Abstract

Herbal medicine plays a pivotal role in Nigeria's health-care system, particularly among non-health professionals, with many individuals relying on traditional remedies for self-medication and disease management. The review aims to identify sources of information on herbal drugs, types of herbal medications commonly used, reasons for their usage, and associated risks. A comprehensive literature search was conducted using electronic databases, including PubMed, Google Scholar, and local Nigerian journals, complemented by gray literature from government health websites and reports. Key terms such as "herbal medicine," "Nigeria," "non-health professionals," and "information accessibility" were employed to identify relevant studies and reports published between 2000 and 2023. The selected materials were analyzed to extract themes surrounding the knowledge and practices of non-health professionals regarding herbal medicine. Findings reveal that non-health professionals primarily rely on traditional healers, family members, and media sources for information. However, these sources often lack scientific evidence, resulting in potential misinformation. Commonly used herbal remedies include moringa, neem, and various local plants, often endorsed for their perceived efficacy and affordability compared to conventional drugs. Despite the cultural acceptance of herbal medicines, significant safety concerns arise from inadequate regulation, potential toxicity, and adverse drug interactions when used concurrently with pharmaceuticals. This review highlights the need for improved regulation, credible information dissemination, and public education regarding herbal medicines to enhance safe practices. Recommendations include collaborating with health authorities to promote awareness and integrating traditional healers into formal health-care systems. By shedding light on the current state of herbal drug information accessibility and usage, this study underscores the importance of addressing gaps in knowledge to safeguard public health in Nigeria.

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1. Introduction

Herbal medicine has been an essential component of traditional health care in Nigeria, with many individuals relying on plant-based remedies for various ailments.[1] Despite the growing accessibility of modern health-care services, herbal drugs remain a significant part of the health-care landscape, particularly among non-health professionals. This continued use of herbal medicine is often driven by affordability, cultural beliefs, accessibility, and the perception that herbal remedies are safer or more natural than conventional pharmaceuticals.[2] Furthermore, in the absence of sufficient health-care infrastructure, especially in rural areas, many Nigerians turn to herbal remedies for self-medication, disease prevention, and long-term management of chronic conditions.[3]

Nigeria has over 500 ethnic groups, each with unique traditions of healing that involve the use of local plants, animal products, and minerals for medicinal purposes.[4] For many Nigerians, particularly those in rural communities, herbal medicine remains the first choice for managing common ailments such as malaria, coughs, fevers, and even chronic diseases such as hypertension and diabetes.[3]

While herbal drugs are widely used, the sources of information about these remedies and their patterns of usage among non-health professionals are not always well-documented or scientifically supported. Much of the knowledge about herbal medicines is passed down through generations in a largely informal, oral tradition.[4] In recent years, however, the rise of digital platforms such as social media and online health blogs has made herbal drug information more accessible, although this information can sometimes be unregulated or unreliable.[5] The National Center for Complementary and Integrative Health is a United States governmental agency that provides information on herbal products, dietary supplements, and complementary health approaches. In addition, PubMed is a database of scientific articles, including research on herbal medicines, where studies on the efficacy and safety of various herbs can be found.[6] The Herbal Medicine Comprehensive database offers detailed monographs on hundreds of herbal products and supplements, including effectiveness, interactions, and potential safety concerns. The American Herbalists Guild provides resources for herbal practitioners and those interested in herbal medicine, including articles, webinars, and a directory of clinical herbalists. Furthermore, Dr. Duke's Phytochemical and Ethnobotanical Databases under the United States Department of Agriculture Data for Agricultural Plants enable comprehensive searches of plants, chemicals, bioactivities, and ethnobotany using scientific or common names.[7]

In regions where there is a high burden of diseases, whether communicable (malaria and tuberculosis) or non-communicable (diabetes and hypertension), access to modern health-care facilities and medications may be limited. Herbal medicine often provides an accessible alternative, as many communities may have traditional knowledge of local plants and their medicinal uses.[8] Some herbal treatments are believed to have preventive properties, which can be appealing in areas with high disease rates. Individuals may use herbal remedies to strengthen their immune systems or manage symptoms of chronic diseases, thereby attempting to reduce their risk of both communicable and non-communicable diseases.[9]

Non-health professionals – individuals who have not received formal training in medicine – are a significant demographic of herbal drug users in Nigeria. They typically obtain their knowledge of herbal remedies from various informal sources, including traditional healers, family members, local markets, and increasingly, the Internet.[10] However, the lack of formal education in pharmacology, toxicology, and health sciences may contribute to improper usage, including incorrect dosages and unsafe combinations of herbal drugs with conventional medicines.[8] Furthermore, while herbal medicines are often believed to be "natural" and therefore safer, concerns about the safety, efficacy, and quality control of these products persist. A significant number of herbal medicines in Nigeria are produced without standardized guidelines or regulation, raising questions about their safety and potential for adverse effects.[11,12]

Given that many people are now using herbal medicine, safety issues are also becoming a significant concern. Certain herbal medicines have been implicated in several critical adverse events relating to cardio-, neuro-, and nephrotoxicities as well as cancers.[13,14] Toxicity due to herbal medicines may occur, and the severity may vary depending on the herb or herbal material, preparation, and user, ranging from minor to severe, and sometimes fatal. Adulterations and concomitant use of herbal medicines with conventional medicines constitute another area of attention; thus, there is a need for strict regulation, enlightenment, and control.[15]

This narrative review was constructed through a comprehensive literature search using electronic databases, including PubMed, Google Scholar, and local Nigerian journals, complemented by gray literature sourced from government health websites and reports published within 2018 – 2023 to ensure the relevance and currency of information.[16] Sources from different geographic regions and ethnic groups, particularly within Nigeria, were included to capture a comprehensive view of herbal practices. Research focusing on various aspects such as cultural beliefs, preparation methods, regulatory frameworks, and health implications of herbal medicine was incorporated to provide a well-rounded analysis.[16]

This narrative review aims to explore the accessibility of herbal drug information and examine the patterns of herbal drug use among non-health professionals in Nigeria. Understanding these factors is crucial for addressing the potential risks associated with unregulated use and for fostering informed decision-making among herbal drug users.

1.1. Rationale for the study

Focusing on non-health professionals in the study of herbal drug usage in Nigeria is significant for several key reasons, particularly the widespread practice of self-medication, the growing popularity of herbal drugs, and the central role of traditional knowledge in shaping health practices. Understanding these factors is crucial for addressing potential risks and improving the safety and efficacy of herbal medicine use in Nigeria.

1.2. Research objectives

The primary objective of this study is to explore the accessibility of herbal drug information and the usage patterns among non-health professionals in Nigeria. Specifically, the study aims to:

(i) Identify and categorize the sources and types of information available to non-health professionals regarding herbal medicines
(ii) Analyze the sociocultural factors influencing how different ethnic groups utilize herbal remedies
(iii) Assess the implications of herbal medicine practices on public health strategies and policies.

1.3. Research questions

The following research questions were constructed to guide the study:

(i) What are the common sources and types of information regarding herbal drugs in Nigeria that are accessible to non-health professionals?
(ii) What are the herbal drug usage patterns among non-health professionals across different ethnic groups in Nigeria?
(iii) What factors influence the choice and application of herbal remedies among non-health professionals?
(iv) How do cultural beliefs and practices shape the understanding and use of herbal medicine within various ethnic groups?
(v) What implications do these practices have for public health and policy in Nigeria?

1.4. Significance of the study

The findings of this research are expected to provide valuable insights into the roles that herbal medicine plays in the lives of non-health professionals in Nigeria. Understanding the dynamics of plant usage can aid public health practitioners, policymakers, and researchers in formulating appropriate strategies that encompass both herbal and conventional medicine. In addition, this research may serve as a foundation for further studies aimed at documenting and preserving traditional knowledge systems, enhancing the status of herbal medicine as a legitimate form of health care, and promoting cultural understanding amid globalization.

1.4.1. Widespread self-medication practices in Nigeria

One of Nigeria's most notable health behavior trends, especially among non-health professionals, is the widespread practice of self-medication. According to various studies, a large proportion of the Nigerian population resorts to self-medication when dealing with health issues, often due to limited access to formal health-care services, high treatment costs, or long waiting times at health-care facilities.[18] For many individuals, especially in rural areas where access to health care is minimal, herbal remedies provide a practical and affordable alternative.

Non-health professionals, who lack formal medical training, often rely on their personal experiences, cultural beliefs, or community knowledge when selecting and using herbal medicines. This can lead to inappropriate self-diagnosis, incorrect dosage, or the misuse of remedies that may interact negatively with other treatments. In addition, the lack of professional oversight in the administration of herbal medicine can result in adverse health outcomes. Understanding how and why self-medication is so prevalent, and how non-health professionals obtain their information, is crucial for identifying potential risks and formulating interventions to promote safer practices.[19]

1.4.2. Growing popularity of herbal drugs

Herbal medicines have become increasingly popular in Nigeria, with many individuals turning to plant-based remedies for their perceived health benefits. This popularity is primarily driven by factors such as the perceived "natural"

properties of herbal remedies, their accessibility, and affordability. As the cost of conventional pharmaceuticals rises and access to formal health-care remains limited, particularly in rural communities, herbal drugs present an attractive alternative.[20] This trend is reflected in the growing number of herbal products available in markets, both local and urban, as well as the increasing use of herbal medicine for managing common ailments such as malaria, respiratory infections, and digestive disorders.[21]

Non-health professionals, who may have limited knowledge of the potential side effects or interactions of herbal drugs, often rely on informal channels such as family members, friends, or local herbalists to guide their decisions. While many herbal remedies have proven therapeutic benefits, their unregulated use without proper guidance can pose risks, such as the ingestion of toxic plants, contamination with harmful substances, or improper dosage.[17] Given that herbal medicine is widely used across Nigeria, especially by non-health professionals, it is essential to focus on this group to understand their motivations, behaviors, and the sources of information they rely on to develop effective education and regulation strategies.[21]

1.4.3. Role of traditional knowledge

In Nigeria, traditional knowledge of herbal medicines is a valuable resource passed down through generations. Indigenous healers, herbalists, and community elders play a vital role in preserving and disseminating this knowledge. Many non-health professionals rely heavily on this traditional knowledge, either from elders in their families or local herbalists who have gained informal expertise through experience. This knowledge base is crucial for understanding how herbal remedies are selected and used, as well as the cultural significance attached to them.[22]

However, while traditional knowledge offers invaluable insights, it is often unverified by scientific research. As a result, herbal medicine usage among non-health professionals can sometimes be based on anecdotal evidence, which may not always be reliable or safe. Furthermore, with the increasing influence of social media and digital platforms, disseminating unverified or misleading information about herbal remedies has become more common.[23] It is more important to study how non-health professionals acquire herbal drug information and how traditional knowledge is integrated into their health-care decision-making.[24]

This study aims to bridge the gap between traditional knowledge and modern scientific understanding by focusing on non-health professionals. Exploring how traditional knowledge guides herbal drug use can provide valuable insights into how Nigerian communities perceive, value, and utilize herbal remedies. It also allows for a better understanding of the need for education, regulation, and standardized practices in using herbal medicines, ensuring that the benefits of traditional knowledge are maximized while minimizing potential risks.[25]

1.4.4. Need for education and regulation

While herbal medicine plays a critical role in the health-care system, especially in underserved regions, there is a significant need for formal education and regulation. Non-health professionals, despite their frequent use of herbal remedies, often lack formal education on the proper use, potential side effects, and safe practices surrounding these substances. They may be unaware of the risks of incorrect dosage, herbal-drug interactions, or potential contamination.[11] By focusing on this demographic, the study can inform policymakers, health-care professionals, and regulatory bodies about the areas where education and regulation are most needed.

As herbal medicine becomes more widely used, there is an urgent need for government and regulatory bodies to implement stronger oversight mechanisms, such as ensuring the safety, efficacy, and quality of herbal products on the market. Understanding the information-seeking behavior of non-health professionals and their usage patterns will help identify gaps in knowledge and how information about herbal medicine can be better disseminated to the public.[26]

2. Historical, cultural, and social relevance of herbal drugs

The use of herbal medicine in Nigeria dates back thousands of years, with indigenous knowledge passed down through generations. Each ethnic group in Nigeria has its own set of medicinal plants and traditional healing practices.[13] For instance, the Yoruba, Igbo, and Hausa people have rich traditions of herbal therapy, often documented in oral histories, folklore, and ritual practices.[14] Early Nigerian herbalists, known as babalawos (Yoruba) or dibias (Igbo), were revered as experts in the use of plant-based medicine, and many of their practices have survived into the modern era, albeit with evolving methods.[13] Babalawos and dibias are custodians of extensive traditional knowledge of herbal remedies, rituals, and spiritual healing practices. They are pivotal in preserving indigenous medical knowledge, often passed down through generations. In contemporary settings, they may engage in educational efforts to train younger generations about medicinal plants and traditional healing methods.[14] Both roles are essential for maintaining

cultural identity and spirituality. They continue to perform rituals and practices that reinforce community bonds, which are especially important in globalization and the encroachment of Western medical paradigms. Some babalawos and dibias adapt to changes by incorporating modern health practices into their traditional methods. They may work alongside physicians or incorporate conventional health knowledge into their consultations, offering a hybrid form of care that draws on traditional and modern medicine.[15]

Before the colonial period, African societies had developed extensive knowledge of their local flora and fauna, using these resources for medicinal, dietary, and ritual purposes. As Western medicine and colonial influence took hold in Nigeria, herbal medicine continued to coexist with these new systems, often providing an affordable and culturally familiar alternative to pharmaceutical drugs.[17] Colonization resulted in the exchange of botanical knowledge between cultures. European colonizers often documented and adapted traditional remedies encountered in colonized regions, leading to the development of hybrid medicinal systems. For example, many African herbal practices have influenced herbal medicine in the Americas through the transatlantic slave trade, integrating various therapeutic approaches and plants that persist in contemporary use.[18]

In Nigerian society, the practice of herbal medicine is not only a health care option but a deep-rooted cultural practice. It is often tied to family and community life, with remedies being shared among relatives, neighbors, and local healers.[16] In rural areas, where access to formal health care may be limited or prohibitively expensive, herbal medicines remain the first line of defense against illness. In these communities, knowledge of herbal drugs is passed from one generation to the next, typically through oral communication, storytelling, and hands-on mentorship.[20]

Herbal medicines are used to treat many ailments, from common illnesses, such as colds and fevers, to more serious conditions such as malaria, high blood pressure, and diabetes.[18] Plants such as moringa, bitter leaf, and neem have also gained popularity for their purported health benefits, including detoxifying the body, boosting the immune system, and managing chronic diseases.[21] The widespread cultural acceptance of herbal remedies often stems from their integration into religious practices, with many plants having symbolic significance or being associated with spiritual healing.[22] For example, in Hinduism, tulsi (*Ocimum sanctum*) is regarded as a sacred plant, representing purity and divinity. It is often grown near homes and temples. Tulsi is used in meditation and worship practices for its calming effects and is believed to purify the mind and enhance spiritual awareness.[23] *Aloe vera* is regarded as a symbol of health and healing across many cultures. It is commonly called the "plant of immortality" in ancient Egyptian culture.

Socially, herbal medicine is an economic asset in Nigeria, providing livelihoods for many people, including herbalists, farmers, traders, and researchers. The growing market for herbal products has led to the establishment of small-scale businesses, with herbal medicine manufacturers and marketers catering to both local and international consumers. Furthermore, herbal products are often sold in local markets, where they are marketed alongside conventional medications, contributing to a flourishing informal economy.[24]

3. Common types of herbal medicines used in Nigeria

Herbal medicines in Nigeria encompass various plant species, each used for specific therapeutic purposes. Some of the most commonly used herbal remedies are summarized in Table 1.

3.1. Bitter leaf (*Vernonia amygdalina*)

3.2. Moringa (*Moringa oleifera*)

Moringa is often referred to as the "miracle tree" due to its numerous health benefits. The leaves, seeds, and pods of moringa are consumed for their high nutritional value and medicinal properties. It is believed to help improve immune function, lower blood sugar levels, reduce inflammation, and combat malnutrition.[30] Moringa is also used to treat conditions such as high blood pressure, asthma, and digestive issues. However, high doses of moringa leaf powder may cause stomach upset and diarrhea. In addition, the roots of the moringa tree contain compounds that can be toxic if consumed in large amounts. Pregnant women, in particular, should avoid moringa roots as they may cause abortion.[31]

3.3. Neem (*Azadirachta indica*)

Neem, also known as "Indian Lilac," is another widely used plant in Nigeria. It is revered for its anti-bacterial, anti-viral, and anti-fungal properties. The leaves and bark of the neem tree are used to treat a range of conditions, including skin infections, malaria, and as a detoxifying agent.[32] Neem is also used as a natural pesticide, demonstrating its multifaceted uses in Nigerian communities. High doses of Neem leaf extracts have been associated with renal toxicity in experimental settings.[33]

Table 1. Summary of key herbal medicines, their uses, and potential risks

Herbal medicine	Traditional uses	Potential risks
Moringa (*Moringa oleifera*)	Used for treating high blood pressure, diabetes, malnutrition, and inflammation	High doses may lead to digestive issues, electrolyte imbalances, or liver toxicity
Ginger (*Zingiber officinale*)	Commonly used for nausea, digestion issues, and inflammation	It can cause heartburn, gastrointestinal irritation, or interaction with blood thinners
Garlic (*Azadirachta indica*)	Used for treating malaria, skin infections, and as a detoxifier	Excessive use may cause kidney damage, diarrhea, or low blood pressure.
Soursop (*Graviola*)	Believed to treat cancer, inflammation, and digestive problems	Long-term use can cause nerve toxicity and may interact with chemotherapy drugs
Hibiscus (*Hibiscus sabdariffa*)	Used to lower blood pressure, treat fever, and improve digestion	May lower blood pressure, too much can cause dizziness or fainting in some individuals
Bitter leaf (*Veronia amygdalina*)	Commonly used for treating diabetes, malaria, and digestive issues	Excessive consumption may lead to liver toxicity or digestive upset
Turmeric (*Curcuma longa*)	Used as an anti-inflammatory agent for joint pain and digestive issues	It may cause gastrointestinal issues or interact with blood-thinning medications
Peppermint (*Mentha piperita*)	Used to relieve indigestion, headaches, and muscle pain	It can cause heartburn or allergic reactions, especially in people with sensitive skin
Lemon grass (*Cymbopogon citratus*)	Used to treat fever, high blood pressure, and as a calming agent	Overuse may lead to digestive issues or allergic reactions

3.4. Ginger (*Zingiber officinale*)

Ginger is a commonly used herb in Nigerian households, both as a spice in cooking and as a medicinal remedy. It is known for its anti-inflammatory, antioxidant, and anti-nausea properties. Nigerians use ginger to treat digestive issues, alleviate nausea, reduce joint pain, and improve circulation.[34] High doses of ginger can lead to heartburn, diarrhea, and stomach upset. Furthermore, ginger possesses blood-thinning properties and may increase bleeding risk when consumed with anticoagulant medications.[35]

3.5. Garlic (*Allium sativum*)

Garlic is widely used for its anti-microbial and cardiovascular benefits. It is commonly employed in treating colds, flu, and respiratory problems, as well as for managing hypertension and cholesterol.[36] The active compounds in garlic, such as allicin, are believed to have significant health benefits. Garlic has anti-platelet properties, which can increase the risk of bleeding, particularly if taken with anticoagulant medications. High doses of garlic can lead to gastrointestinal distress, including heartburn, gas, and diarrhea. Some individuals may experience allergic reactions to garlic, including skin rashes and respiratory issues.[37]

3.6. African mango (*Irvingia gabonensis*)

African mango, or bush mango, is used primarily for weight management and improving metabolic health. The seeds are believed to help control cholesterol, reduce blood sugar levels, and assist in weight loss. This herb has gained attention in both local and international markets due to its potential anti-obesity properties. High doses of African mango may cause stomach upset and diarrhea.[38]

3.7. Soursop (*Annona muricata*)

Soursop is a tropical fruit tree known for its sweet, tangy flavor and medicinal benefits. Traditionally, the leaves and fruit are used to treat infections, fever, and digestive problems. Soursop is also believed to have anti-cancer properties. It contains acetogenins, which have demonstrated cytotoxic effects against cancer cells.[39] Some studies suggest that soursop may have neurotoxic effects linked to the compounds present in the seeds, which can potentially contribute to neurological disorders, including Parkinson's disease.[40]

3.8. Holy basil (Tulsi) (*Ocimum sanctum*)

Known for its aromatic properties, the holy basil is revered in many cultures for its health benefits.

It is traditionally used for stress relief, respiratory issues, and immunity enhancement. It is often consumed as tea or in powder form. Holy basil contains important phytochemicals such as eugenol and rosmarinic acid, contributing to its adaptogenic and anti-inflammatory properties.[41] Holy basil may have blood-thinning properties, which can increase bleeding risk in individuals taking anticoagulant medications.[42]

3.9. Pawpaw (*Carica papaya*)

The pawpaw tree is indigenous to tropical America but is widely cultivated in Nigeria. Traditionally, pawpaw leaves

are used to treat malaria, whereas the fruit is eaten for its digestive benefits and nutritional value. Pawpaw is rich in enzymes such as papain, which aids digestion.[43] Some individuals may have allergies to pawpaw, leading to skin rashes and gastrointestinal disturbances.[44]

3.10. African bird pepper (*Capsicum frutescens*)

The African bird pepper is a hot pepper widely used in Nigerian cuisine and traditional medicine. It is traditionally used to stimulate appetite, alleviate pain, and treat respiratory ailments. Capsaicin, the active compound in peppers, is known for its analgesic and anti-inflammatory properties.[45] While African bird pepper may help stimulate appetite, excessive consumption may lead to irritation of the gastrointestinal tract, causing pain or discomfort.[45]

3.11. Black cumin (*Nigella sativa*)

Black cumin seeds have been used in traditional medicine for centuries. In Nigerian herbal practices, they are used for various ailments, including asthma, diabetes, and inflammation. Thymoquinone is a prominent bioactive compound in black cumin, known for its antioxidant, anti-inflammatory, and anti-cancer properties.[46] Although generally safe, black cumin may cause allergic reactions in some individuals, including rashes and respiratory issues.[47]

4. Sources of herbal drug information

4.1. Traditional healers and herbal practitioners

In Nigeria, local herbalists and traditional healers often serve as the primary source of herbal drug information for many people. Traditional healers play a central role in disseminating herbal medicine information within communities.[48] They often pass down knowledge through generations and are trusted by many individuals in Nigeria for health advice. However, the challenge is ensuring that the knowledge shared is based on safe practices and accurate information.[49]

4.2. Family and peer networks

Many individuals receive information about herbal remedies from family members or friends, particularly in rural areas where formal health care may be less accessible. This knowledge is typically passed down through cultural and familial practices.[50]

4.3. Media (Radio, television, and newspapers)

Media outlets, including radio, television programs, and newspapers, serve as essential sources of information about herbal drugs. These platforms may present both traditional and scientific perspectives on the benefits and risks of herbal treatments.[50]

4.4. Internet and online platforms

With the rise of digital technology, the Internet has become a major source of information on herbal drugs, especially among younger populations. Social media platforms, websites, and online health forums are popular platforms for learning about herbal remedies, though the reliability of the information varies.[51] Many herbal practitioners and researchers have blogs or social media pages where they share insights and recent developments in herbal medicine. Examples include health-focused platforms on Instagram, Twitter, or YouTube. There are several online platforms that provide access to herbal drug information, including articles, research papers, and encyclopedias.[52] The National Center for Complementary and Integrative Health offers resources related to herbal medicines and dietary supplements, including efficacy and safety information. HerbMed is an interactive database of scientific information on herbal medicine, covering various herbs, their effects, and traditional uses. Duke's Phytochemical and Ethnobotanical Database provides detailed information on the phytochemistry and ethnobotany of plants, including their traditional uses. Reputable organizations and governmental agencies often provide guidelines and research on herbal medicines. In addition, the World Health Organization offers reports and guidelines on herbal medicine worldwide.[53]

However, misinformation about herbal medicine persists. This misinformation includes exaggerated claims of efficacy, which involve overstating the benefits of herbal medicines, suggesting they are cures for serious diseases or conditions without scientific backing. Examples include claims that an herb can cure cancer or reverse diabetes. Misinformation can also arise from claims regarding the sourcing and quality of herbal products. For example, some products may be marketed as "100% pure" or "wildcrafted" when they are not. Consumers may inadvertently purchase poor-quality or contaminated products, which can pose health risks. Misinformation about sourcing can undermine trust in herbal practices and lead to skepticism among consumers. Unregulated products are often marketed with little oversight regarding their safety and efficacy. Moreover, consumers might encounter herbal supplements with vague labels and unverified claims. The use of unregulated supplements can lead to health risks due to contamination, incorrect dosing, and inadequate labeling, potentially harming users and eroding trust in herbal medicine.[54]

4.5. Health-care providers (Doctors, pharmacists, and nurses)

Although non-health professionals may not often rely on health-care providers for information about herbal

drugs, some individuals may seek advice from medical professionals, particularly when combining herbal medicines with conventional treatments.[55]

4.6. Books and academic journals

Some individuals, particularly those with higher education or an interest in herbal medicine, may turn to academic publications, textbooks, and other scholarly sources to learn about the use of herbal drugs. However, the accessibility of such resources can be limited in rural areas.[56]

4.7. Government and health agency publications

Government and health agencies are crucial in regulating herbal medicines to ensure safety, efficacy, and proper labeling. Public health agencies, such as the Nigerian Ministry of Health or the World Health Organization, occasionally provide guidelines and reports on herbal medicines. These documents might include safety recommendations and regulatory information, although access to such publications can be limited in some regions.[57] Other key regulatory agencies include Nigeria's National Agency for Food and Drug Administration and Control (NAFDAC), which is responsible for regulating and controlling food, drugs, and herbal products in Nigeria. Its mandate includes ensuring that herbal medicines meet safety and quality standards before they enter the market. Herbal products must be registered with NAFDAC, which involves submitting documentation that demonstrates the product's safety, efficacy, and quality. This includes evidence, trial, or traditional use documentation. NAFDAC enforces good manufacturing practice (GMP) standards for manufacturers of herbal medicines. This ensures that products are consistently produced and controlled according to quality standards. Herbal products must have accurate labeling that includes information on ingredients, recommended dosages, usage instructions, and potential side effects. Claims on the label must be substantiated. In addition, NAFDAC conducts post-market surveillance to monitor the safety and efficacy of herbal products that are already on the market. This includes tracking adverse reactions and ensuring compliance with regulatory standards.[58]

4.8. Workshops and community health outreach programs

Non-professional individuals may also gain herbal drug information through community workshops or health outreach programs conducted by non-governmental agencies, community health workers, or local governments. These initiatives often aim to educate the public on both the benefits and risks of herbal medicine.[59]

4.9. Health fairs and herbal medicine conferences

Health fairs and conferences often feature sessions on the use of herbal drugs, where individuals can learn from experts, including researchers, traditional healers, and product manufacturers.[60]

5. Perceived benefits of herbal medicine

The perceived benefits of herbal medicines in Nigeria are shaped by both traditional beliefs and practical experiences. Many Nigerians view herbal medicine as a safer, more natural alternative to conventional pharmaceutical drugs. There is a widespread belief that herbal remedies are less likely to cause side effects, particularly when compared to synthetic medications, which may be seen as harsh or artificial. For example, plants such as bitter leaf are considered to have purifying and detoxifying properties, making them popular choices for managing chronic illnesses like diabetes and hypertension.[61]

Herbal medicines are also perceived to have cultural and spiritual significance, often used for physical healing and emotional and spiritual well-being. Many herbal remedies are associated with rituals, prayers, and spiritual practices, further strengthening their place in Nigerian society. For instance, herbalists may offer prayers while preparing or administering certain remedies, reinforcing the belief that healing is a holistic process that involves both physical and spiritual elements.[62]

In addition, herbal medicines are often viewed as affordable, with many remedies being freely available in local markets or from family members and community healers. This affordability and accessibility make herbal drugs particularly attractive in low-income and rural communities where people may face financial constraints or lack access to formal health-care services.[63]

6. Comparison of Internet sources to traditional sources in herbal medicine information

The rise of the Internet as a primary source of information has transformed how individuals access knowledge about herbal medicines. While the Internet offers convenience and a wealth of resources, there are notable differences in reliability when compared to traditional sources such as academic journals, books, and professional medical advice.[64]

6.1. Accessibility and availability

The Internet provides immediate access to an extensive range of information on herbal medicines, including articles, blogs, forums, and research papers. This

accessibility allows users to gather information quickly from multiple perspectives without physical access to libraries and databases.[65] On the other hand, traditional sources such as academic journals and books may require specific access (e.g., subscriptions or physical libraries), as they are curated and peer-reviewed, often providing more authoritative content. This can limit immediate availability but ensures a higher information standard.[66]

6.2. Quality of information

The quality of information on the Internet can vary significantly. Many websites may offer anecdotal experiences or personal opinions rather than scientifically validated information. Factors such as author credentials, publication reviews, and bias must be critically evaluated.[67] Regarding traditional sources, academic journals and books generally undergo rigorous peer review and editorial processes. This enhances the reliability of the information being presented. Traditional sources often include references to empirical research and clinical studies, providing a solid foundation for claims made about herbal medicines.[68]

6.3. Credibility and trustworthiness

On the Internet, websites with information on herbal medicines may lack credentials, and consumers must be vigilant in determining the credibility of the source. Resources such as Wikipedia, personal blogs, or non-professional health websites may present misinformation or unverified claims, leading to potential health risks.[69] In contrast, traditional sources, such as published scientific research and medical literature from reputable institutions, uphold established standards of evidence-based medicine. These traditional sources typically come from professionals with expertise in the field, thereby increasing their trustworthiness.[70]

6.4. Evidence-based information

While some online platforms, such as databases (e.g., PubMed and National Center for Complementary and Integrative Health) and health organization websites (e.g., World Health Organization), provide evidence-based guidance, many internet resources emphasize anecdotal evidence and personal testimonials. This can lead to the promotion of unproven or ineffective herbal medicine.[71] Whereas traditional sources, such as academic publications, prioritize systematic reviews of literature, clinical trials, and empirical evidence. These sources are key to validating the efficacy and safety of herbal products, providing insights grounded in scientific research.[72]

6.5. Bias and commercial influence

Many Internet sources may contain bias – products may be marketed with inflated claims to increase sales. In addition, blogs and websites funded by herbal product companies may present information skewed to favor their product.[73] In contrast, peer-reviewed articles and publications affiliated with academic institutions are generally free from commercial influence. They focus on unbiased evidence to present a balanced view of the subject matter.[74]

6.6. User engagement and community feedback

Online platforms often encourage user interaction through comments and forums, allowing for shared experiences and recommendations. While this can provide valuable insights, it is essential to exercise caution, as personal stories may not reflect broader clinical outcomes.[75] On the other hand, traditional sources typically do not allow for community feedback; their information is presented as established knowledge. While this structure promotes reliability, it may lack the immediate engagement that users find beneficial online.[76,77]

7. Usage patterns of herbal drugs among non-health professionals

The patterns of herbal drug use in Nigeria vary across different demographic groups, but there are several common trends.

(i) Self-medication: A significant proportion of non-health professionals use herbal drugs for self-treatment, particularly for common ailments such as headaches, body pain, coughs, and gastrointestinal issues. This pattern is primarily due to the perceived safety, affordability, and availability of herbal remedies.[78]

(ii) Chronic disease management: Individuals suffering from chronic conditions such as diabetes, hypertension, and arthritis often use herbal remedies either as a primary treatment or as an adjunct to conventional medicine. However, the lack of standardized dosing and quality control in herbal products may lead to safety concerns.[79]

(iii) Preventive health: In some cases, herbal drugs are used for preventive purposes, such as boosting immunity or detoxifying the body. These uses are often based on cultural beliefs and are sometimes promoted by herbal practitioners.[80]

(iv) Cultural beliefs and trust: Traditional healing practices are often trusted more than modern medicine in certain communities. Many people prefer herbal medicine because they believe it is "natural," and therefore safer, or because it is part of their cultural heritage.[81]

8. Challenges in herbal drug information accessibility

Accessing reliable information on herbal drugs remains a significant challenge, especially in resource-limited settings. These challenges are caused by several factors, as discussed below.

(i) Misinformation and lack of regulation. One of the key challenges in Nigeria is the lack of regulation in the herbal drug sector. Many herbal products are marketed with exaggerated claims, and the absence of standardized guidelines means consumers may be exposed to unsafe or ineffective treatments.[82,83]

(ii) Quality control issues. Herbal products in Nigeria are often unregulated, resulting in issues with product quality, contamination, and adulteration. This makes it difficult for consumers to trust the information they receive regarding the safety and efficacy of herbal remedies.[84,85]

(iii) Illiteracy and language barriers. In rural areas, where the majority of herbal drug users reside, illiteracy rates are high. This limits the accessibility of written information, which may be available in formal languages such as English, but is not readily understandable to everyone. This gap exacerbates the reliance on word-of-mouth information, which may not always be accurate.[86]

(iv) Lack of scientific evidence. Many herbal medicine users in Nigeria do not have access to scientific studies or clinical trials that validate the effectiveness of their treatments. The absence of robust scientific evidence makes it harder for non-health professionals to distinguish between effective and ineffective remedies.[87] Research shows that most Nigerians rely on traditional medicine, including herbal remedies. A study by Albrecht and Smith[90] indicated that about 70% of respondents in their survey used herbal remedies regularly. However, they often lack sufficient knowledge about the active ingredients and their effects. This signals a gap in understanding the scientific basis of the herbal medicines they consume. In addition, a survey conducted by Anis and Nasir[91] explored the awareness of herbal medicine among rural and semi-urban populations in Nigeria and reported that many respondents had limited access to detailed information about these remedies. Specifically, they noted that more than 60% of participants relied heavily on traditional knowledge passed down through families rather than scientific studies or literature.

9. Potential solutions or mitigation strategies for herbal drug information accessibility challenges

Addressing the challenges associated with herbal drug information accessibility requires a multifaceted approach that involves various stakeholders, including governments, health-care professionals, traditional practitioners, and the community.[90] Below are potential solutions and mitigation strategies for enhancing access to reliable information about herbal medicines.

9.1. Strengthening regulatory frameworks

Implementing strong policy and regulatory frameworks that guide the production, distribution, and use of herbal medicines is essential.

(i) Establish comprehensive regulations. Governments should develop and enforce strict regulations to ensure the safety, quality, and efficacy of herbal medicines. This includes requiring registration of herbal products with health agencies, such as NAFDAC in Nigeria.

(ii) GMPs. Promoting adherence to GMP standards among herbal product manufacturers to ensure consistency and reliability in herbal medicines can increase consumer trust.[91]

9.2. Enhancing public education and awareness

Challenges associated with the accessibility of information on herbal medicines can also be mitigated through public education.

(i) Community education programs. Implementation of educational campaigns about the safe use of herbal medicines. These programs can involve workshops, seminars, and local health fairs to educate the community about the potential benefits and risks associated with herbal remedies.

(ii) Integration into formal education. Incorporating herbal medicine training into medical and health professional curricula can empower future health-care providers to understand and respect traditional practices. This could foster better communication with patients who use herbal remedies.[92]

9.3. Increasing access to research and reliable information

Regarding access to information about herbal remedies, strategies to increase this include:

(i) Digital literacy initiatives. Developing programs to improve digital literacy, particularly in low-income or rural communities, will help individuals access reliable online resources and scientific literature related to herbal medicine.

(ii) Online resource development. This can be achieved by creating centralized online platforms that provide vetted, evidence-based information about herbal medicines, detailing their uses, potential side effects, and scientific research. This could also include partnerships with universities, health organizations, and government agencies.[93]

9.4. Promoting collaboration between traditional and modern medicine

The collaboration between traditional and modern medicine can also facilitate increased access to information about herbal drugs.

(i) Integrating health-care models. Encourage collaboration between traditional healers and health-care providers. Creating integrative health-care models can enhance patient care by blending traditional knowledge with modern medical practices.
(ii) Interdisciplinary workshops. Organizing workshops and forums where traditional practitioners and health-care professionals are able to share knowledge and experiences can lead to mutual respect and understanding.[94]

10. Factors influencing usage patterns

Several factors influence the usage patterns of herbal medicine within the community. These include:

(i) Economic factors. Cost is a significant determinant of herbal drug use. Herbal drugs are often seen as more affordable than pharmaceutical drugs, especially in low-income communities.[95]
(ii) Perceived safety and efficacy. The widespread belief in the effectiveness of herbal medicine, especially in rural areas, plays a central role in its continued use. Many users report that herbal treatments are effective, though these claims are often based on personal experience rather than clinical evidence.[96]
(iii) Accessibility. Herbal drugs are often more accessible than conventional medicines, particularly in remote or rural areas where health-care facilities may be scarce.[97]
(iv) Cultural factors. In many Nigerian communities, herbal medicine is considered a culturally significant practice. This cultural attachment to traditional medicine influences its use and acceptance.[98]
(v) Trust in herbalists. Trust in local herbalists or traditional healers plays a significant role. People often seek advice from these practitioners based on their knowledge, reputation, and the experience of others in the community.[99]

11. Policy and regulatory framework

The Nigerian government has made notable strides in regulating herbal medicine, recognizing its significance in the country's health-care system and the need to ensure safety and efficacy. The recent policy developments and efforts by the Nigerian government, specifically through agencies such as the NAFDAC and other related entities, to regulate herbal medicine[100] are discussed below.

11.1. Regulatory framework enhancement

The enhancement of the regulatory framework is being achieved through two main approaches.

(i) Updated guidelines for herbal medicines. NAFDAC has been actively reviewing and updating its guidelines for registering and regulating herbal products. These guidelines emphasize the need for scientific evidence to support claims made by herbal products and require comprehensive documentation regarding quality control, safety, and efficacy.[101]
(ii) Traditional Medicine Policy. In 2020, NAFDAC and the Federal Ministry of Health unveiled the National Policy on Traditional Medicine. The policy aims to integrate traditional medicine practices, including herbal medicine, into the national health-care system, ensuring that they are recognized, regulated, and practiced safely.[102]

11.2. Collaborative effort with traditional healers

Regarding collaborative efforts, NAFDAC has initiated dialogs and training programs that engage traditional healers and herbal practitioners. These initiatives are designed to educate them on regulatory requirements, quality standards, and safe practices in herbal medicine. This collaboration seeks to enhance the credibility of traditional medicine while ensuring consumer safety.[103]

11.3. Promotion of research and development

In recent years, the Nigerian government has emphasized research into medicinal plants, collaborating with universities and research institutions. These efforts aim to validate the efficacy of traditional remedies and document indigenous knowledge. The government has called for more funding and support for studies focused on herbal medicine to promote evidence-based practices.[104]

11.4. Adverse event reporting and safety monitoring

Nigeria's NAFDAC has been developing systems to monitor the safety of herbal products. This includes making provisions for consumers and health-care providers to report adverse reactions associated with herbal medicines. The emphasis on monitoring aims to improve the safety profile of herbal products and enhance public trust.[105]

11.5. Consumer awareness campaign

To combat misinformation and educate the public about herbal medicine, NAFDAC has initiated campaigns to raise awareness of the importance of quality and safety in herbal products. These campaigns provide information about the proper use of herbal medicines, potential interactions with conventional drugs, and the importance of purchasing registered and verified products.[106]

11.6. Collaborations with international organizations

The Nigerian government has sought collaboration with the World Health Organization to align its regulations and practices with international standards. This partnership aims to enhance the credibility of Nigerian herbal medicines globally and improve the quality and safety of herbal treatments.[107]

11.7. Comparison of Nigeria's regulatory framework with international guidelines

Nigeria's regulatory framework for herbal medicine in comparison with international guidelines (notably those from the World Health Organization) and regulatory frameworks in other African countries reveals similarities and differences.[108] NAFDAC regulates herbal medicines in Nigeria by creating guidelines that require herbal products to be registered, manufactured following GMP, and labeled accurately.[109]

The World Health Organization has established the *Traditional Medicine Strategy 2014 – 2023* to promote the safe and effective use of traditional medicine globally. Key components of these guidelines include:

(i) Integration. Encouraging the integration of traditional medicine into national health systems
(ii) Safety and quality. Emphasizing the need for safety, efficacy, and quality through regulation and standards
(iii) Research promotion. Supporting research and development to validate traditional practices and promote evidence-based approaches
(iv) Global standards. The World Health Organization provides guidelines for regulating herbal medicines, advocating for harmonization to facilitate trade and consumer safety.[109]

Regulatory frameworks in other African countries include the South African Health Products Regulatory Authority, which oversees the regulation of medicines, including herbal products.[110] The Medicines and Related Substances Act governs the registration and authorization of herbal medicine. The Kenya Pharmacy and Poisons Board regulates herbal medicines under the Medicines Act.[111] Specific provisions for herbal products require registration and compliance with safety standards. Kenya has developed a National Policy on Traditional Medicine, emphasizing the need for evidence-based development and integration of traditional medicine into health-care services. The Food and Drugs Authority in Ghana regulates herbal medicine by requiring registration and stringent quality control measures.[112-114]

12. Conclusion

This review examines the complexities of herbal medicine within the context of Nigeria, highlighting the regulatory frameworks, cultural significance, and challenges faced in ensuring safe and effective use. By synthesizing current knowledge and identifying gaps in accessibility, regulation, and public understanding, this review contributes to the existing literature in several significant ways.

First, it underscores the critical need for a well-defined regulatory framework for herbal medicines in Nigeria, aligning with international guidelines while considering local cultural contexts. By analyzing Nigeria's regulatory efforts in comparison to successful frameworks established in other African countries, this review provides a roadmap for strengthening existing policies. Consequently, it advocates for implementing practices that can improve safety and consumer trust in herbal products.

Second, this review recognizes the implications of misinformation and the underutilization of traditional knowledge among health-care providers and consumers. It identifies a growing need for educational initiatives to increase awareness and understanding of herbal medicines, ensuring that individuals can access accurate, evidence-based information. This focus on education enhances the discourse surrounding herbal medicine and encourages a more informed public.

Third, this review contributes to ongoing discussions about integrative health approaches by highlighting the vital interplay between traditional practices and modern health care. It advocates for collaborations between traditional healers and health-care professionals, promoting a more comprehensive health-care model that respects cultural heritage while ensuring patient safety.

Finally, the review points toward future research directions, emphasizing the need for empirical studies that evaluate the efficacy and safety of popular herbal medicines. Such research is crucial for validating traditional practices and informing policy decisions.

13. Recommendations

13.1. Clinical efficacy studies

Conducting randomized controlled trials can scientifically validate the efficacy of widely used herbal

remedies for common ailments, such as malaria, diabetes, and hypertension. Research should focus on popular herbs such as *V. amygdalina* (bitter leaf) and *M. oleifera t*o establish evidence-based guidelines for their use. In addition, comparative effectiveness studies can compare the effectiveness of herbal treatments against conventional medical treatments. This research could help determine the best integrative approaches for specific health conditions.

13.2. Safety assessments and toxicology

Monitor the adverse effects by investigating the potential herb-drug interactions of common herbal medicines using pharmacovigilance methods. This is especially important for herbs frequently consumed by patients alongside conventional medications. Moreover, research on the toxicity levels of less-studied herbs and their long-term effects on health, especially those used in high doses or with limited scientific backing, can be conducted to assess the safety of herbal medicine.

13.3. Phytochemical analysis

Identifying and characterizing the active phytochemicals in popular herbal remedies can increase the understanding of the compounds and their mechanisms of action, enhancing the application of these herbs in treatment protocols. In addition, developing methods for standardizing herbal extracts ensures consistency in potency and safety.

13.4. Cultural practices and perceptions

Comprehensive ethnobotanical surveys can be conducted to document the traditional uses of herbal medicines across different ethnic groups in Nigeria. These surveys should focus on understanding how cultural beliefs shape the selection and application of herbal remedies. Moreover, studying public perceptions of herbal medicine, including trust levels, knowledge gaps, and barriers to using herbal remedies, can increase the understanding of these attitudes. This understanding can inform educational campaigns and health interventions.

13.5. Integration with modern health care

Research into effective models for integrating herbal medicine with conventional health-care systems can be performed. Case studies of successful integration in Nigeria and abroad offer insights into how such integration can enhance health practices. In addition, examining the efficacy of training programs that educate health-care providers about herbal medicine is essential, particularly those focusing on the benefits of collaboration with traditional practitioners.

13.6. Community engagement and education

The effectiveness of community health education interventions that promote the understanding of herbal medicine's benefits and risks should be assessed to evaluate how such interventions affect consumer behavior regarding herbal products. Furthermore, there must be an engagement in research methodologies that involve the community in the design and implementation of studies on herbal medicine, ensuring that local knowledge and practices are respected and integrated.

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ORIGINAL RESEARCH ARTICLE

Femtomolar inhibition by a virtually designed molecule: Pseudoeriocitrin as a potent inhibitor

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Abstract

Pseudoeriocitrin is a virtually designed molecule created *in silico* by assuming the formation of oxygen radicals in eriocitrin, resulting in a different geometry. It achieves femtomolar-level inhibition in *in silico* docking studies, demonstrating higher inhibitory efficacy than eriocitrin. This study investigated the mechanisms underlying the extraordinary inhibitory activity of pseudoeriocitrin through a 3D analysis of potential interactions using an *in silico* protein-ligand docking method. Although it is difficult to reach a definitive conclusion, the absence of hydrogen donors renders the pseudoeriocitrin structure highly toxic. The high binding affinity of pseudoeriocitrin, which inhibits various proteins at the femtomolar level, with the lowest inhibition constant value of 3.45 fM, is presumably due to its planar structure and the abundance of oxygen radicals, which facilitate the formation of hydrogen bonds with atoms in the active site of the proteins. This study is the first to demonstrate the structure-activity relationship of pseudoeriocitrin through *in silico* docking method. The results indicate that the large core structure, abundance of oxygen atoms, planar geometry, and femtomolar-level inhibition are interrelated. The chemical properties resulting from these unique biological properties should be examined from multiple perspectives. In addition, further research is required to explore the synthesis of non-radical pseudoeriocitrin.

Keywords: Eriocitrin; Femtomolar inhibition; Molecular docking; Pseudoeriocitrin

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1. Introduction

In a world experiencing rapid advancement in health service technologies, helminthic infections remain a serious medical concern. According to recent data, approximately two billion people worldwide are infected with at least one species of soil-transmitted helminthes.[1] Given the side effects of synthetic anthelmintic drugs, which include the frequent recurrence of infections in areas with poor sanitation – particularly among pre-school-aged children – the need for alternative treatments to replace synthetic drugs has become increasingly important. Consequently, the discovery of new anthelmintics with fewer side effects is a crucial task. Oxyurid nematode infections, which are transmitted orally and often recur due to autoinfection, predominantly affect children and lead to developmental disorders.[2] It is estimated that 400 million people

worldwide were infected with *Enterobius vermicularis* in 2015.[3]

β-tubulin, carnitine o-palmitoyltransferase-2 (CPT 2), and fumarate reductase have recently been the primary antinematodal targets for the development of several anthelmintics, such as albendazole, mebendazole, ivermectin, and thiabendazole. Due to the unknown genome sequence and the lack of crystallized structure of *Syphacia obvelata*-derived proteins, the homology modeling of mitochondrial cytochrome c oxidase (COX) proteins can be useful in *in silico* docking experiments to investigate the antinematodal properties of certain drug candidates against *S. obvelata*.[4] Performing protein-ligand docking simulations using *in silico* molecular modeling is the initial step in developing new drugs. These computational experiments could provide researchers with atomic-level information on the interactions between drug molecules and target proteins. Such experiments are highly valuable in reducing the workload involved in drug development.[5]

Eriocitrin, (2*S*)-2-(3,4-dihydroxyphenyl)-5-hydroxy-7-[(2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-[[(2*R*,3*R*,4*R*,5*R*,6*S*)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxymethyl]oxan-2-yl]oxy-2,3-dihydrochromen-4-one, is an eriodictyol-derived flavonoid glycoside mainly found in lemon peel, citrus pulp, and certain plants, such as thyme and mint.[6] It is formed by the addition of O-β-rutinose at the 7th position of eriodictyol. Eriocitrin exhibits antioxidant, anti-inflammatory, and antiproliferative properties.[7-9] The study by Ferreira *et al.*[10] reported the presence of eriocitrin and its metabolites in various organs and body fluids of rats administered with orange peel extract. The major metabolites of eriocitrin are homoeriodictyol and homo-eriodictyol-7-*O*-glucuronide (hERD-7-*O*-Gluc). The half-life of these metabolites in blood plasma is 3 – 3.2 h. In addition, hesperetin-7-*O*- and hesperetin-3'-*O*-gluconic acid, metabolites of eriocitrin, were detected in both tissue and urine samples of the rats. The concentration of hERD-7-*O*-Gluc reached approximately 8 ng/g in blood plasma 10 h after administration, while that of hERD-4'-*O*-Gluc peaked at approximately 2 ng/g after 6 h, representing the highest concentration in the blood. However, gastrointestinal absorption of eriocitrin was found to be extremely low, with a total bioavailability of <1%.

In our previous *in silico* computational study,[4] we investigated the anthelminthic effect of eriocitrin, whose molecular structure is shown in Figure 1A. Interestingly, we found an additional bond in eriocitrin when studying its possible interactions with target proteins. Further analyses of the eriocitrin derivative in the present study found that pseudoeriocitrin inhibits several proteins at the femtomolar level (inhibition constant, $K_i = 10^{-17}$ mol/L).

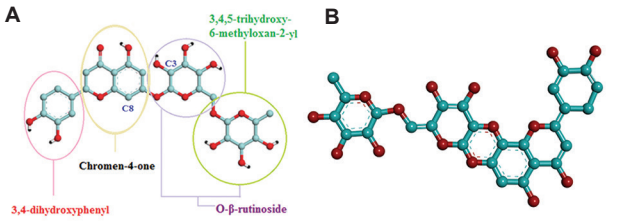

Figure 1. Molecular representation of eriocitrin and pseudoeriocitrin. (A) Molecular structure showing the rings forming eriocitrin. The bond leading to the formation of pseudoeriocitrin is formed between the chromene-4-one ring and the oxygen atom of the hydroxyl group of the chromene-bonded monosaccharide of O-β-rutinoside. (B) Molecular representation of pseudoeriocitrin.

This study aimed to explore the structure and interactions of pseudoeriocitrin, potentially related to its anthelmintic activity. An *in silico* docking study provides insights into inhibition potency, serving as a foundation for new drug synthesis research. In addition, these *in silico* results may assist drug designers interested in the structure-activity relationship of highly potent multi-inhibitors. This study is the first to report a virtual molecule with femtomolar K_i against multiple proteins. Consequently, its interactions with anthelmintic target proteins, researched through *in silico* methods, provide novel and original data. Furthermore, this study is the first to elucidate the structure-activity relationship of a multi-radical virtual molecule capable of multi-inhibition at exceptionally low K_i values.

2. Materials and methods

2.1. Acquisition and preparation of pseudoeriocitrin

Pseudoeriocitrin was retrieved from the FooDB database (www.foodb.ca) as a PDB file in November 2019 (ligand ID: FDB016547). In the PDB file, deposited as eriocitrin in the FooDB database, all Z coordinates were set to 0. This PDB file was converted to a PDBQT file using the AutoDock Tool (ADT).[11,12] When the Z coordinates were 0, the ADT program ignored the hydrogen atoms in the hydroxyl groups and assumed an additional bond in the core structure. This assumption was based on the sufficient distance between the C8 atom in the chromene ring of the ligand and the oxygen atom of the hydroxyl group at the C3 position of the rutinoside group, which allowed for potential bonding (Figure 1). As a result, the generated PDBQT file lacked hydrogen donors. The 3D molecular representation of pseudoeriocitrin is shown in Figure 1B.

2.2. Preparation of proteins

Proteins and enzymes in nematodes that could serve as potential drug targets were chosen. Biovia Discovery Studio 2020 Client[13] and ADT software were used for

protein preparation. For this purpose, target proteins and enzymes found in nematodes, as well as their human homologs with crystallized structures, were obtained from the Brookhaven Protein Databank (http://www.rcsb.org/pdb). These target proteins and enzymes are known targets of anthelmintic drugs, such as albendazole (β-tubulin inhibition), thiabendazole (fumarate reductase inhibition), and certain inhibitors used in *Onchocerca lienalis* infection (carnitine o-palmitoyltransferase inhibition).[14] Human homolog proteins were used to evaluate the selectivity of the inhibitor. The selected proteins were as follows: *Ascaris suum* fumarate reductase (AsFR) enzyme (PDB ID: 4YSX, mitochondrial rhodoquinol-fumarate reductase, resolution: 2.25 Å, bound with NN23 inhibitor);[15] human fumarate reductase (hFR) enzyme (PDB ID: 6VAX, resolution: 2.59 Å);[16] human β-tubulin protein (PDB ID: 6E7C, resolution: 3.65 Å);[17] *Haemonchus contortus* β-tubulin protein (PDB ID: 1OJ0, in complex with ABZ, theoretical structure);[18] rat CPT 2, a target of anthelmintic drug (PDB ID: 2H4T, resolution: 1.90 Å, bound with dodecane [$C_{12}H_{26}$];[19] and PDB ID: 2FW3, resolution: 2.50 Å, in complex with antidiabetic drug ST1326[20]). The work of Taylor *et al.*[14] was used as a reference for identifying some target proteins. Since the crystallized form of β-tubulin from *H. contortus* was unavailable in protein databases, its theoretical structure was used. Ions and ligands, except for cofactors and water molecules, were removed. Missing hydrogen atoms were added, and the residues of the proteins were checked for missing atoms and bonds. After adding all hydrogen atoms, the proteins were optimized using the "Clean Geometry" tool, followed by the Charm forcefield. The optimized proteins were saved in PDB format using Discovery Studio 2020 Client, then opened using ADT to add Gasteiger charges, and finally saved in PDBQT format.

2.3. Homology modeling

The known protein sequences for *S. obvelata* were searched using the UniProt Knowledgebase. Although the COX1 and COX2 proteins from the mitochondrial genome are not known targets of anthelmintics, they were selected because they are vital to oxyurid nematodes. Since the genome sequence of *S. obvelata* and the experimental crystal structure of the *S. obvelata* COX1 (SoCOX1) and COX2 (SoCOX2) proteins are unknown, homology modeling was employed to predict their 3D structures. Proteins from other oxyurid nematodes, *E. vermicularis* β-tubulin (EvTub) protein and *Caenorhabditis elegans* glucose transporter 1 (CeGLUT1) receptor were also *in silico* modeled using homology modeling, as they are essential for nematodes and represent potential drug targets. The homology models and Ramachandran plots are shown in the Appendices. Two web servers, the SWISS-MODEL[21] and Zhang lab I-TASSER,[22-24] were utilized to develop a sequence overlap-based model. The most appropriate 3D structure was selected based on Global Model Quality Estimating (GMQE) and Qualitative Model Energy Analysis (QMEAN) values. For QMEAN, values below 4.0 indicate reliability, while for GMQE, the highest value between 0 and 1 represents the most reliable predicted structure.

2.4. Docking process

Proteins retrieved from the Protein Data Bank or those with 3D structures predicted by homology modeling were docked with ligands using AutoDock4.2.[25] All energies used in the calculation of molecular free binding energy (ΔG) in the AutoDock program were described by Morris *et al.*[25] The formula to calculate free binding energy is as follows:

$$\Delta G = RT\ln K_i \quad \text{(I)}$$

R is the gas constant (R = 8.314 J/K/mol). T represents the temperature of the environment measured in Kelvin. The *Ki* represents half of the substrate concentration required for maximum inhibition of protein-ligand binding.

The grid box size was determined based on the ligand size or the number of torsions. The cofactor of the protein was chosen as the center, or in the absence of a cofactor, the native ligand bound to the protein was placed at the center of the grid box. For the β-tubulin protein docking simulation, the ligand bound to the protein was selected as the center. For the CPT 2 enzyme, the coordinates provided by Taylor *et al.*[14] were used as a reference. Atoms at the active site of the protein were allowed to move freely, while the rest of the protein remained rigid. To dock proteins with their natural ligands in their co-crystallized form, the natural ligands were used as a reference. The dielectric constant was set to 10, the ionic strength to 0.145, the dimensions of the grid box to 60 × 60 × 60, and the grid point to 0.375 Å. Since the number of rotational bonds was <10, the maximum number of generations was set to 27,000 and the maximum number of extensions was set to 2,500,000. The docking procedure was performed using the Lamarckian Genetic Algorithm 4.2. AutoDock 4.2 scoring functions were used to generate ten different conformations for each ligand. After sorting the ligands by their free binding energy, the interactions at the binding site of the ligands were analyzed using ADT and Biovia Discovery Studio 2020 Client.

2.5. Absorption, distribution, metabolism, and excretion (ADME) prediction

SwissADME web server[26] was used to estimate the ADME properties of pseudoeriocitrin and eriocitrin. Their ability to cross the blood-brain barrier, gastrointestinal absorption, and oral bioavailability were evaluated through chemical computation.

The SwissADME website provides users with free and reliable prediction models for various properties, including physicochemical characteristics, pharmacokinetics, drug similarity, and medicinal chemistry relevance. These models incorporate well-established methods such as BOILED-Egg, iLOGP, and Bioavailability Radar. Lipophilicity, molecular size, polarity, solubility, flexibility, and saturation properties are used to generate a radar plot.[26] These properties are the fundamental criteria to determine whether the predicted physicochemical and pharmacokinetic values of a bioavailable compound fall within reasonable limits.

According to the bioavailability radar, a bioavailable compound should meet the following criteria: molecular weight between 150 and 200 g/mol, topological polar surface area between 20 and 130 $Å^2$, lipophilicity (XLOGP3) between −0.7 and +5.0, carbon fraction in sp^3 hybridization (a saturation marker) >0.25, solubility (logS) <6,[26] water solubility score falls between 1 and 3 (on a scale of 1 – 5, with 1 indicating the highest solubility and 5 indicating the lowest solubility), and number of rotatable bonds between 0 and 9.[27]

3. Results

3.1. Evaluation of potential interactions between pseudoeriocitrin and rat carnitine palmitoyl transferase 2

One of the findings of this study was that the K_i of pseudoeriocitrin against rat CPT 2 (PDB ID: 2H4T) was 15.83 fM. This result suggests that pseudoeriocitrin may act as a highly potent CPT 2 inhibitor. However, it should be noted that pseudoeriocitrin is a virtual molecule and is not accessible in existing databases. Therefore, it can only serve as a reference for the design of *de novo* drug candidate molecules.

Studies on the potential interactions between pseudoeriocitrin and the rat CPT 2 enzyme (PDB ID: 2H4T) revealed a significant number of interactions with the residues, as illustrated in Figure 2A. While most of these residues were apolar amino acids, the polar hydrophilic residues such as serine and tyrosine (TYR486) were located in close proximity to pseudoeriocitrin, forming aromatic interactions. Figure 2B demonstrates that cyclic side chain residues, such as PHE131 and PHE134, contribute to hydrogen bond formation rather than aromatic interactions. Five hydrogen bonds were predicted through Biovia 2020 Client (as indicated by the green dashed lines in Figure 2B).

One of the most important factors in the interactions of pseudoeriocitrin is the chemical attraction arising from the oxygen atoms on each ring of the ligand. As illustrated in Figure 2B, residues LEU599, GLY600, PHE134, PHE131, SER588, and TYR486 formed hydrogen bonds with the oxygen atoms on the ligand. Specifically, PHE134 formed two hydrogen bonds with the oxygen atoms of the ligand, one at a distance of 2.75 Å and the other at 3.29 Å, while SER588 formed a hydrogen bond at a distance of 1.81 Å. In addition, PHE602 formed an aromatic interaction with one of the two rings in the center of the ligand and an amide-π interaction with the other ring. PRO and ALA residues also formed π-alkyl interactions with two different rings of the ligand. Notably, each ring of the ligand had at least one π–alkyl interaction.

The hydrophobicity of the region formed by the residues surrounding pseudoeriocitrin is crucial because it directly affects the interactions of the ligand. Figure 3 illustrates the hydrophobic and hydrophilic regions around pseudoeriocitrin in the binding site of rat CPT 2. The presence of polar residues outside the hydrophobic surface, particularly the side chains of amino acids, such as alanine, valine, glycine, phenylalanine, and leucine, created hydrophilic areas adjacent to the apolar residues that border one side of the ligand. For comparison, the interactions between eriocitrin and the residues of rat CPT 2 are illustrated in Figure 4. In this case, a different structure of CPT 2 was used (PDB ID: 2FW3), which is distinct from the CPT 2 (PDB ID: 2H4T) used in Figures 2 and 3. Meanwhile, Figure 5 depicts the varying potential interactions between pseudoeriocitrin and the residues of rat CPT 2 (PDB ID: 2FW3). Video A1 illustrates the localization of pseudoeriocitrin in the enzyme CPT 2 (PDB ID: 2FW3). The surface of the CPT 2 (PDB ID: 2FW3) enzyme and the potential ligand entry site are demonstrated in Figure 6A, while Figure 6B displays the position of pseudoeriocitrin after it has entered the CPT 2 enzyme.

3.2. Evaluation and comparison of potential interactions between pseudoeriocitrin and AsFR or hFR

Pseudoeriocitrin exhibits a strong binding affinity to AsFR, with a K_i value of 512 pM, making it highly effective in inhibiting this enzyme. The positions of pseudoeriocitrin on AsFR and hFR enzymes are illustrated

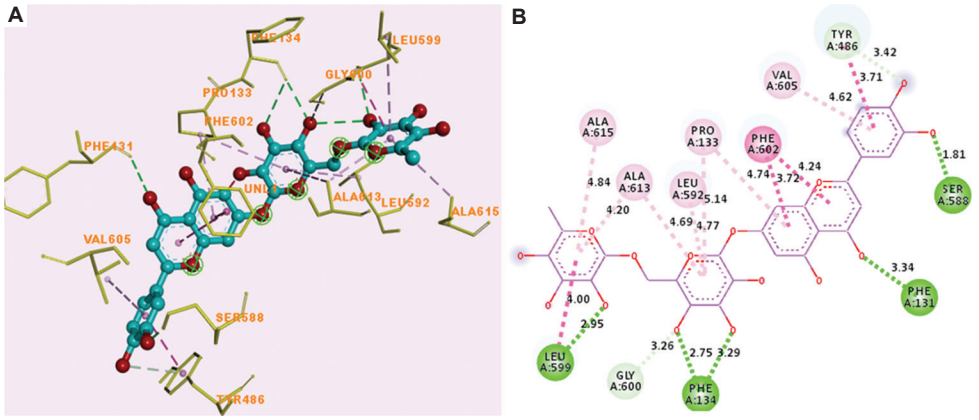

Figure 2. Potential interactions between pseudoeriocitrin and rat carnitine palmitoyl transferase 2 (CPT 2, PDB ID: 2H4T). (A) Carbon atoms of pseudoeriocitrin are illustrated in blue, oxygen atoms in red, and the residues with which it interacts are represented by the yellow stick model. (B) 2D representation of the interactions between pseudoeriocitrin and the rat CPT 2 enzyme (not shown in the figure because the AutoDock4.2 program does not display the abnormal bond formation in the defective molecule on the coordinate axis of the dlg file).

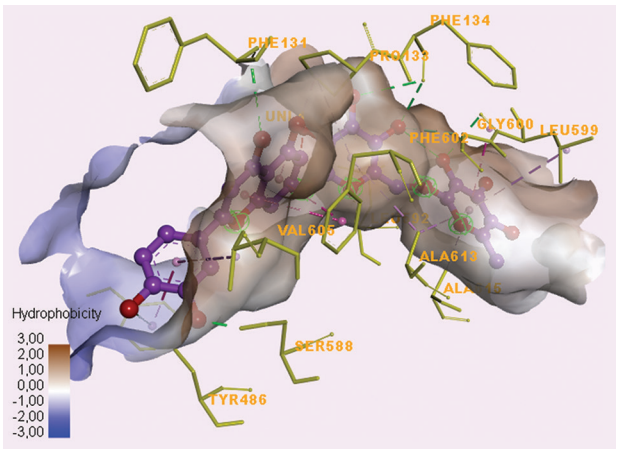

Figure 3. Representation of surface hydrophobicity around pseudoeriocitrin in the binding site of rat carnitine palmitoyl transferase 2 enzyme. The blue surfaces represent the most hydrophilic regions, while the brown surfaces represent the hydrophobic regions. The hydrophilic region at the bottom is where the tyrosinyl and serinyl residues are located and stand out.

in Figures 7 and 8. A closer examination of these figures reveals the bi-oxygenated cyclic structure (the ring at the center of the ligand), which results from unusual bond formation and leads to the structure of pseudoeriocitrin. Video A2 illustrates the localization and interactions of pseudoeriocitrin in hFR.

The potential interactions of pseudoeriocitrin with AsFR are illustrated in Figure 9. Hydrogen bond formations were predicted with five different residues, and a π-sigma bond with THR81 is likely to occur. Similarly, the potential interactions of pseudoeriocitrin with hFR are illustrated in Figure 10. We identified 12 predicted hydrogen bond formations, indicating strong inhibition with hFR.

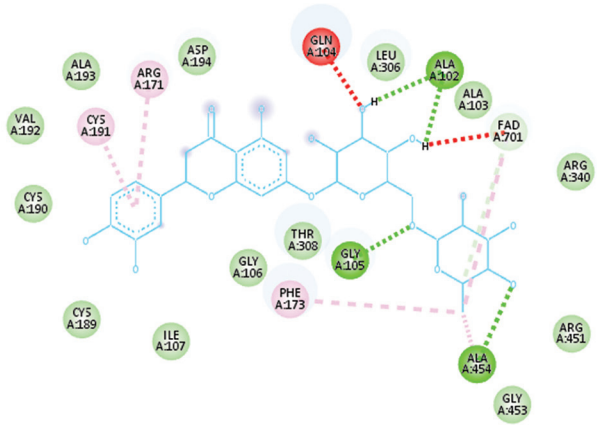

Figure 4. Localization of eriocitrin in rat carnitine palmitoyl transferase 2 (PDB ID: 2FW3)

3.3. Evaluation of potential interactions between pseudoeriocitrin and *C. elegans* Glucose transporter 1

The position of pseudoeriocitrin in CeGLUT1 and the interacting residues are shown in Figure 11. Docking simulations indicate that pseudoeriocitrin exhibits a strong binding affinity for CeGLUT1, with a predicted ΔG value of −17.18 kcal/mol. To further illustrate the docking simulation, Video A3 provides a visualization of the interaction process. The 3D structure of CeGLUT1 was predicted through homology modeling, as shown in Figure A1.

3.4. Evaluation of potential interactions between pseudoeriocitrin and *S. obvelata* cytochrome c oxidase 1

The ring structure formed by an additional bond between the chromene ring of pseudoeriocitrin and the

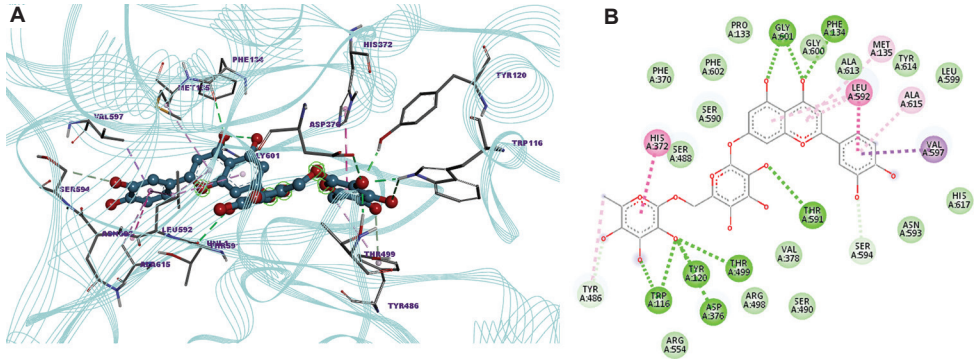

Figure 5. Potential interactions between pseudoeriocitrin and rat carnitine palmitoyl transferase 2 (PDB ID: 2FW3). (A) The 3D representation of the model. (B) The 2D representation of the model.

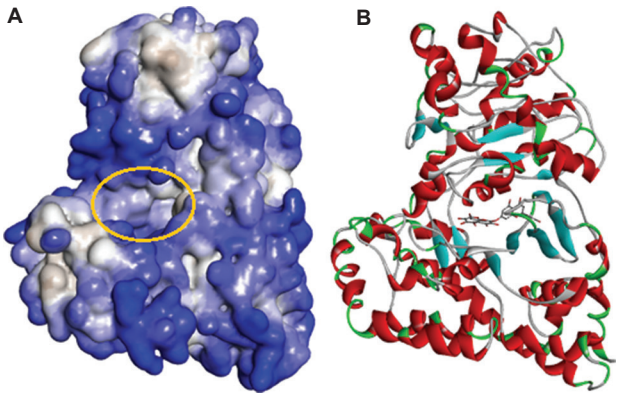

Figure 6. Position of pseudoeriocitrin in carnitine palmitoyl transferase 2 (PDB ID: 2FW3). (A) In the representation of the enzyme surface, the cavity in the orange circle was presumed to be the entry cavity of pseudoeriocitrin into the enzyme. In the figure, blue regions represent hydrophilic regions, and brown regions represent hydrophobic regions. (B) This version is the same model as in (A) but without a surface. Pseudoeriocitrin, demonstrated with the stick model, positions in the center, which is the lowest energy region.

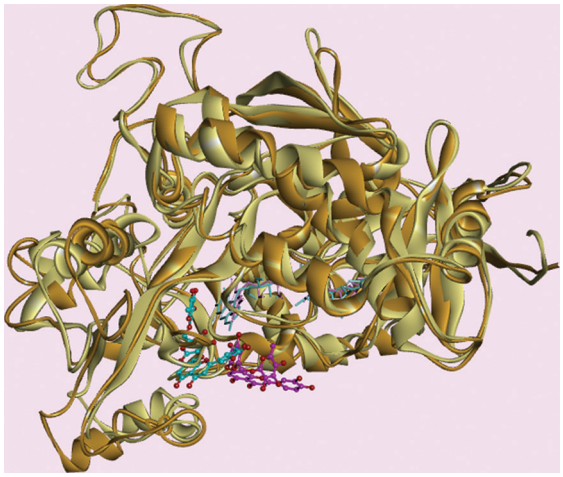

Figure 7. A model of pseudoeriocitrin, *Ascaris suum* fumarate reductase (AsFR), and human fumarate reductase (hFR). The pseudoeriocitrin molecules are shown in their positioning within the enzymes AsFR and hFR so that their localization in both different proteins can be compared. AsFR is represented by an orange ribbon, Flavine-adenine-dinucleotide (FAD) of AsFR by a purple stick model, hFR by a cream ribbon, FAD of hFR by a dark green stick model, pseudoeriocitrin docked to AsFR by a fuchsia ball-stick model, and pseudoeriocitrin docked to hFR by a turquoise ball-stick model.

rutinoside structure allowed pseudoeriocitrin to interact with SoCOX1, as shown in Figure 12. To enhance the understanding of these interactions, Video A4 provides a dynamic visualization. In addition, the corresponding homology models and Ramachandran plots of SoCOX1 and SoCOX2 are presented in Figure A2.

As shown in Figure 12A, the L-shaped structure formed by the rings of the ligand is strongly attracted to ALA62. In addition, the rhamnosyl ring of the rutinoside group at the other end of the ligand interacts with the cyclic side groups of residues HIS39 and HIS40 through aromatic interactions. Furthermore, VAL107 on another α-helix interacts with the same group from the opposite direction, allowing the ligand to fit well into its position. The key chemical interactions illustrated in Figure 12B are the hydrogen bonds formed between the oxygen atoms of the ligand and the residues HIS39 and GLY104. Moreover, ALA62 forms six interactions with different positions of the ligand.

3.5. Docking of pseudoeriocitrin with all proteins

We performed docking experiments with ligands 3 times due to a structural change in the molecule, which we initially attributed to the optimization procedure. However, we later discovered the actual reason to be the presence of erroneous molecules in the FooDB database from which the ligand was sourced. In the various molecular structures of pseudoeriocitrin, the formation of oxygen radicals and the differing geometries contributed to the molecule achieving a good score. Tables 1 and 2 present the docking results of pseudoeriocitrin. The docking procedure was repeated

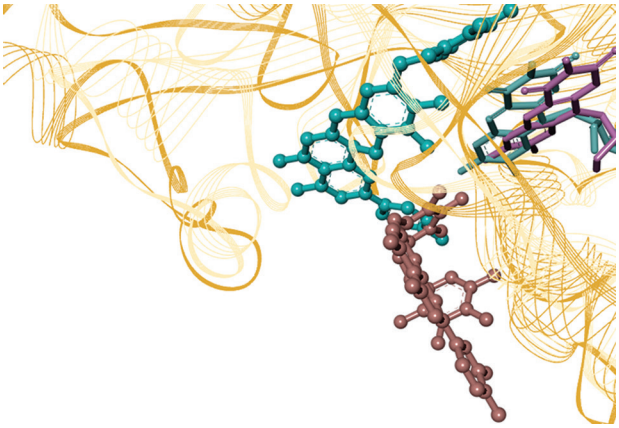

Figure 8. The position of pseudoeriocitrin molecules in *Ascaris suum* fumarate reductase (AsFR), and human fumarate reductase (hFR). Flavine-adenine-dinucleotide is shown in purple and blue with a stick model. The isoalloxazine ring is closely located to the pseudoeriocitrin. Pseudoeriocitrin in AsFR is shown with a light-pink ball and stick model. Pseudoeriocitrin at the docking points of hFR is represented by a turquoise ball-and-stick model, where they are located at the lowest energy level.

twice for pseudoeriocitrin (except the first docking with SoCOX1). As a result of the repeated computations, we obtained different values for the free binding energy at the end of the docking process.

According to Tables 1 and 2, neither eriocitrin nor pseudoeriocitrin could bind to any β-tubulin protein (1OJ0, 6VAX, and EvTub) tested in this study. The homology model and Ramachandran plot of EvTub are shown in Figure A3. However, pseudoeriocitrin did inhibit 1OJ0 (*H. contortus* β-tubulin), albeit with extremely low free binding energy. This indicates that pseudoeriocitrin does not have a toxic effect on β-tubulin. In general, β-tubulin inhibition is associated with the prevention of cell division, which is why β-tubulin inhibitors are utilized in both anthelmintics and anticancer drugs. While pseudoeriocitrin may not directly block cell division, it does inhibit several crucial enzymes in nematodes, such as SoCOX1, SoCOX2, CeGLUT1, and AsFR. Therefore, pseudoeriocitrin can induce cell death in nematodes at low concentrations that may be tolerated by the human body,

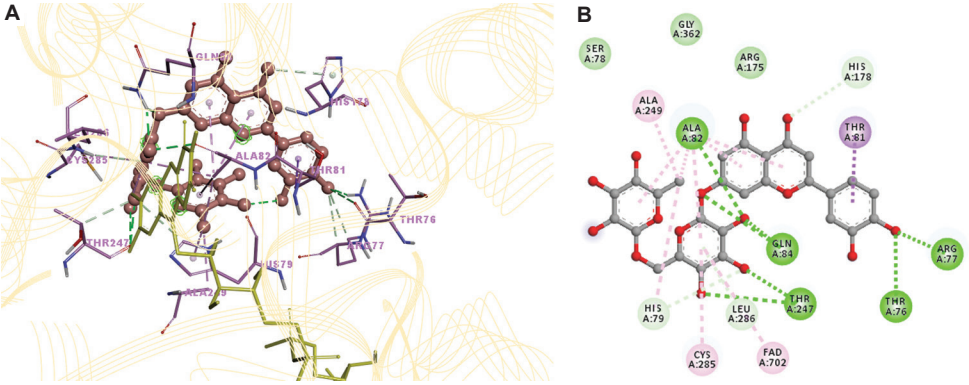

Figure 9. Potential interactions between pseudoeriocitrin and *Ascaris suum* fumarate reductase. (A) The 3D representation of the model. (B) The 2D representation of the model.

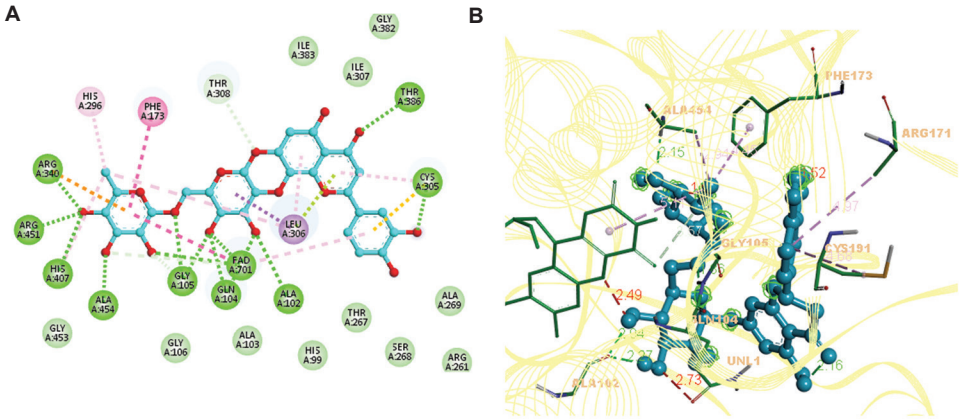

Figure 10. Potential interactions between pseudoeriocitrin and human fumarate reductase. (A) The 2D representation of the model shows the faulty bond that leads to the formation of pseudoeriocitrin. The oxygen atom opposite the LEU306 residue, represented by the purple ball in the figure, bonds with chromene to form an abnormal cyclic structure. (B) The 3D representation of the model.

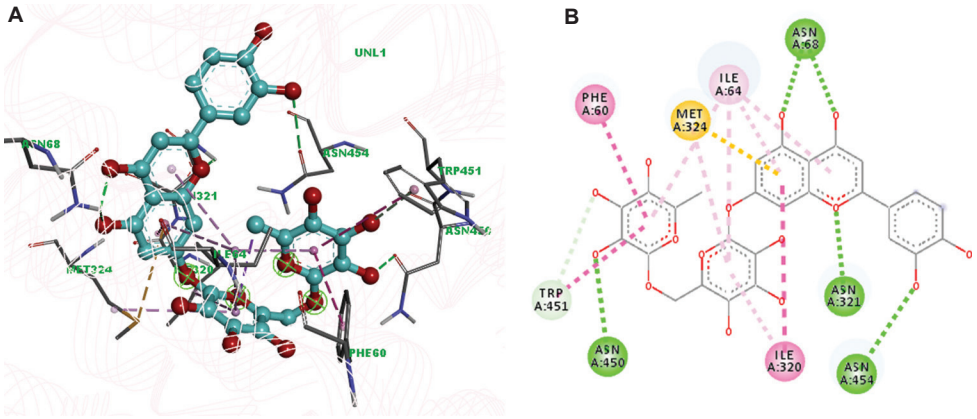

Figure 11. Potential interactions between pseudoeriocitrin and *Caenorhabditis elegans* Glucose transporter 1 (CeGLUT1). (A) 3D representation of pseudoeriocitrin is represented by the turquoise ball-and-stick model, interacting residues by the thin stick model, and protein by the powdery pink strip ribbon model. (B) 2D representation of pseudoeriocitrin and CeGLUT1 interactions.

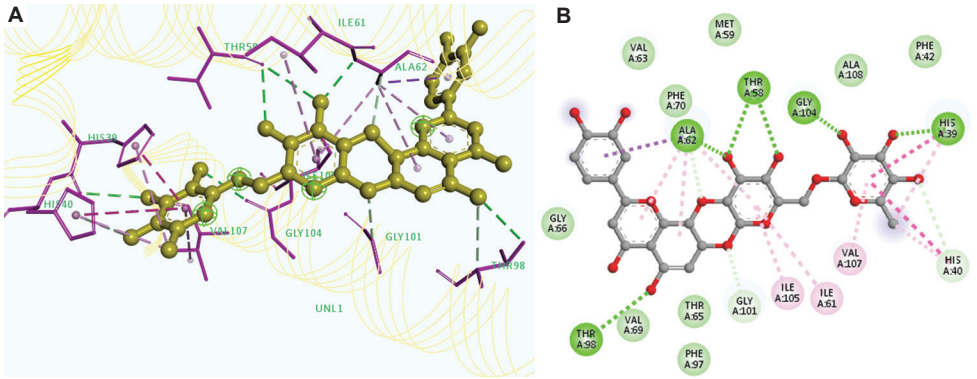

Figure 12. Potential interactions between pseudoeriocitrin and *Syphacia obvelata* cytochrome c oxidase 1 (SoCOX1). (A) Pseudoeriocitrin is represented by yellow balls and sticks, interacting residues are represented by thin purple sticks, dashed lines represent the interactions, and the secondary structure of the protein is represented by a cream-colored strip ribbon model. (B) The 2D representation of the model clearly shows the abnormal structure of pseudoeriocitrin. Notes: Dark green short-distance dashed lines represent hydrogen bonding; Light green long-distance dashed lines represent polar interactions; Pink dashed lines represent π-alkyl bonding; Purple color dashed line represents the π-sigma bond.

Table 1. Docking results of eriocitrin and pseudoeriocitrin (ΔG values [kcal/mol])

Molecule	1OJ0	2H4T	4YSX	6VAX	SoCOX1	SoCOX2	6E7C	Ev Tub	CeGLUT1	2FW3
Eriocitrin	+15.60	−8.43	−6.62	−12.87	−5.92	−3.92	+72.30	+104.90	−6.61	−9.72
PE (in first docking)	−3.21	−18.83	−13.84	−12.30	-	−8.70	+169.70	+118.60	−8.62	−12.17
PE (in second docking)	+3.67	−18.09	−12.67	−18.45	−16.93	−11.22	+49.10	+52.50	−17.18	−19.73

Notes: 1OJ0 represents *Haemonchus contortus* β-tubulin; 2FW3 represents rat carnitine o-palmitoyltransferase in complex with antidiabetic drug ST1326; 2H4T represents rat carnitine o-palmitoyltransferase bound with dodecane; 4YSX represents *Ascaris suum* fumarate reductase; 6E7C represents human β-tubulin; 6VAX represents human fumarate reductase.
Abbreviations: CeGLUT1: *Caenorhabditis elegans* Glucose transporter 1; EvTub: *Enterobius vermicularis* β-tubulin; PE: Pseudoeriocitrin; SoCOX1: *Syphacia obvelata* cytochrome c oxidase 1; SoCOX2: Syphacia obvelata cytochrome c oxidase 2.

potentially through radical scavenging and modulation of the immune system.

The anthelmintic drug target, rat CPT, serves as a chokepoint enzyme in developing new anthelmintic drugs because its substrate indirectly affects the survival of nematodes. Rat CPT inhibitors have been effectively used in eliminating *O. lienalis*.[14] Pseudoeriocitrin inhibits CPT irreversibly, but not covalently. Therefore, this inhibition, which occurs at the femtomolar level, does not have a permanent effect on the host organism.

The selectivity index for pseudoeriocitrin was calculated to be 152,542, comparing the SoCOX1 enzyme to the SoCOX2 enzyme based on their K_i values. The 3D structures of both enzymes were predicted using homology modeling through the SwissModel web server. This *in silico* analysis indicates that pseudoeriocitrin is more effective at inhibiting the SoCOX1 enzyme than the SoCOX2 enzyme.

Pseudoeriocitrin inhibits both AsFR and hFR homolog enzymes. In this case, the selectivity of pseudoeriocitrin for nematode FR is lower than that for human FR, making it less ideal as a ligand for FR inhibition.

Interestingly, pseudoeriocitrin was initially predicted to penetrate the blood-brain barrier, exhibit a high absorption rate in the gastrointestinal tract, and bind to certain cytochrome enzymes that are not inhibited by eriocitrin (SwissADME results for pseudoeriocitrin are shown in Figures 13 and A4). In the subsequent study on the same molecule, the SwissADME web server could not provide a prediction, as the molecular weight exceeded 500 g/mol. The most significant finding in Figure 13A is that pseudoeriocitrin is identified as a multiradical. This radical structure is associated with toxicity and binding ability. However, pseudoeriocitrin is not present in the ZincDatabase. Given its high free binding energy, the interactions related to pseudoeriocitrin are intended to be used in the discovery of new anthelmintics.

4. Discussion

Recent *in silico* studies[28] demonstrated that a new interaction can be formed within a morin molecule by calculating and comparing the enthalpy changes necessary for the conformational change that enables an intramolecular bond. This new conformation allows morin to enhance its radical scavenging activity while adopting a planar structure. As a flavone, morin achieves a planar extension of its flavone core, leading to the formation of a ring, that is, parallel to this core. This condition mirrors the flavone structure examined in our study. The bonds that form between the flavone core and the rutinoside group increase the planar area made up of cyclic structures. Consequently, this arrangement enables the hydroxyl groups of the molecule to create a significant amount of hydrogen bonds with the target proteins, thereby enhancing its inhibitory effect.

Another study demonstrated that modifications of the isoleucyl-tRNA synthetase inhibitor mupirocin can enhance its inhibitory effect.[29] New inhibitors, developed based on modified mupirocin combined with an amino acid side chain, demonstrated a much stronger inhibition of isoleucyl-tRNA synthetase, with dissociation constant (K_d) values of 10 – 12 fM, whereas the parent compound mupirocin inhibited the same enzyme with a K_d value of 140 pM. Similarly, pseudoeriocitrin, a modified form of eriocitrin, demonstrates much higher inhibition

Table 2. Docking results of eriocitrin and pseudoeriocitrin (*Ki* values)

Molecule	1OJ0	2H4T	4YSX	6VAX	SoCOX1	SoCOX2	6E7C	Ev Tub	CeGLUT1	2FW3
Eriocitrin	-	663.49 nM	14.13 μM	370.31 pM	45.64 μM	1.34 mM	-	-	14.24 μM	75.23 nM
PE (in first docking)	2,270.00 μM	15.83 fM	71.76 pM	971.51 pM	-	417.70 nM	-	-	479.82 nM	1.19 nM
PE (in second docking)	-	55.00 fM	512.00 pM	29.86 fM	389.40 fM	59.40 nM	-	-	257.26 fM	3.45 fM

Notes: 1OJ0 represents *Haemonchus contortus* β-tubulin; 2FW3 represents rat carnitine o-palmitoyltransferase in complex with antidiabetic drug ST1326; 2H4T represents rat carnitine o-palmitoyltransferase bound with dodecane; 4YSX represents *Ascaris suum* fumarate reductase; 6E7C represents human β-tubulin; 6VAX represents human fumarate reductase.
Abbreviations: CeGLUT1: *Caenorhabditis elegans* Glucose transporter 1; EvTub: *Enterobius vermicularis* β-tubulin; PE: Pseudoeriocitrin; SoCOX1: *Syphacia obvelata* cytochrome c oxidase 1; SoCOX2: *Syphacia obvelata* cytochrome c oxidase 2.

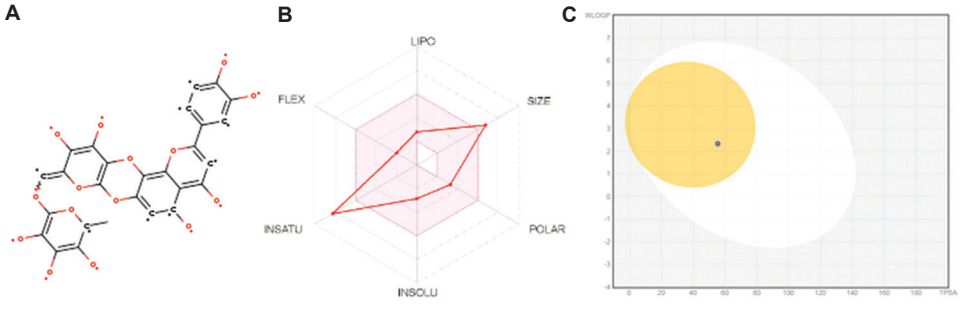

Figure 13. Swissabsorption, distribution, metabolism, and excretion graphical results of pseudoeriocitrin. (A) Molecular structure of pseudoeriocitrin. (B) Radar plot of pseudoeriocitrin. (C) The ability of pseudoeriocitrin to penetrate the blood-brain barrier.

efficacy than eriocitrin. However, the high binding affinity of pseudoeriocitrin to several proteins tested in this study raises concerns about its potential toxicity. If the femtomolar inhibition effect of pseudoeriocitrin is attributed to its chemical properties, we predict that this high level of inhibitory affinity may be due to the following characteristics:

(i) The heterocyclic center structure exhibits a planar geometry
(ii) The core structure of the ligand (the combined cyclic structures at the center) is broad and comprises four rings
(iii) The side chains attached to the core structure feature hydroxyl groups or oxygen atoms
(iv) The positioning of the 3,4,5-trihydroxy-6-methyloxan-2-yl and 3,4-dihydroxyphenyl groups is perpendicular to the plane of the core structure
(v) The center of the ligand is rigid over a wide area, and the side groups are connected to the heterocyclic center through sigma bonds.

The presence of radical oxygen atoms in pseudoeriocitrin contributes to the formation of multiple hydrogen bonds. Further research is required to determine if normal double-bonded oxygen atoms can produce a similar inhibition effect.

In a previous study by Ramalingam *et al*.,[30] a new drug candidate named isopropyl1-benzoyl-4-(benzoyloxy)-2,6-diphenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (IDPC) was synthesized and characterized using Fourier transform infrared spectroscopy (FT-IR) and nuclear magnetic resonance (NMR) techniques. The compound was then investigated through molecular docking to assess its affinity for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) receptors. The analysis revealed frontier orbital energies and a low energy gap, indicating a tendency for intramolecular charge transfer and excellent bioactivity for the compound. The study also demonstrated the presence of hydrogen bonding, covalent and non-covalent interactions, and electron delocalization within the molecule. The strong binding affinity observed between the active sites of the SARS-CoV-2 main protease receptor and the IDPC ligand was attributed primarily to hydrogen bonding and π-cationic interactions involving the phenyl ring and carbonyl oxygen groups.[30] In the present study, *in silico* predictions also suggest a potential connection between oxygen radicals and strong binding affinity.

Common limitations of *in silico* docking arise from the assumption that the environment in which chemical interactions are predicted is stationary. In reality, the biological environment is dynamic and changes over femtoseconds. This environment is full of various solvents and thousands of different molecules which are often not considered in docking. However, these factors may influence protein movement, the probability of the protein encountering the ligand, and the potential energy involved. In addition, different molecules, including water, exhibit significant energy variations due to continuous vibrational and rotational motions. The modes of atomic motion are typically excluded from the calculation used to determine free binding energy. Temperature fluctuation in the environment and the time required for the protein to reach its minimum energy state are also overlooked in docking simulations. In the future, enhanced simulation capabilities may allow for more comprehensive analyses within the same process.

Experimental results are crucial for understanding crystalline structures and translating them into the computational realm through software, such as Gaussian. This enables a comparison of theoretical and practical study results regarding their consistency. In a thorough experimental study by Gatfaoui *et al*.,[31] 1,3-Benzenedimethanaminium bis(trioxonitrate) ($BD[NO_3]_2$) was synthesized and characterized, with its biological activity – particularly its antibacterial activity – was predicted by molecular docking. Highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) analyses were performed to elucidate charge transfer within the molecule. Molecular electrostatic potential (MEP) was calculated to examine the intermolecular hydrogen bond interactions in detail. The study is significant as it demonstrates the consistency between the experimental and computational results. The findings indicate that *in silico* docking simulations can be supported by characterization techniques such as X-ray diffraction (XRD) and FT-IR. Furthermore, HOMO-LUMO analyses should be included in the accuracy test of the targeted chemical structure. In this study, various fungal proteins were used as targets for docking, which were carried out with 10 poses, through the iGEMDOCK program, similar to our study. The results revealed numerous π-anion and π-alkyl interactions, including charge transfer, in the binding region of $BD(NO_3)_2$ with target proteins, as well as hydrogen bonds involving various atoms. The presence of aromatic structures and oxygen atoms in the ligand played an important role in facilitating these interactions. Overall, aromatic rings significantly contributed to the aromatic interactions and increased binding affinity in our study.

Oxygen-rich polyphenols are the active ingredients in many drugs due to their ability to reversibly inhibit enzymes. However, phenolic compounds containing

oxygen radicals are highly reactive and can trigger a contagious radical attack. In this study, we discovered that molecules with a high abundance of oxygen radicals can form multiple hydrogen bonds. The geometry of the molecule also plays a significant role in this process. However, reducing molecules will transform these radicals into more stable molecules. In contrast, when there are high levels of oxygen radicals within a molecule – as seen in pseudoeriocitrin, for example – this neutralization can take considerably longer than other radical molecules. Non-radical oxygen, on the other hand, cannot position themselves in such geometries because the atom is unable to accommodate additional oxygen if it is already double-bonded to carbon. The most significant advantage of this radical molecule is its potential for femtomolar inhibition, suggesting that it may be useful for further investigation, especially *in vitro*, for cancer research. When examining the structure of anticancer drugs, such as bleomycin, we cannot help but wonder why such a multiradical should not be explored for use against solid tumors.

The molecular structures, HOMO-LUMO energy, electronic property, reactivity, and MEP of the main components in the essential oil of *Phlomis bruguieri* Desf. were analyzed in a previous study.[32] The study focused on the most abundant molecules present in the essential oil, which include caryophyllene oxide, β-pinene, 1,8-cineole, α-cubene, and β-caryophyllene molecules, to evaluate their interactions with water through theoretical calculations. In all examined molecules, the electrostatic potential was predominantly determined by the oxygen atoms, which serve as reactive sites for electrophilic attack. For β-caryophyllene, caryophyllene oxide, and 1,8-cineole, the introduction of a water molecule increased the size of the energy gap. This suggests that adding water to these systems slightly altered the energy gap values of the studied substances. Similarly, the introduction of water into eriocitrin may affect its energy gap and stability. Therefore, it would be beneficial to investigate this assumption using the methodology outlined in the study by Akman *et al.*[32]

Planar molecular geometry and the presence of electron-rich oxygen atoms offer significant benefits for ligands when fitting into protein cavities and interacting with surrounding residues. The multi-ring core structure of planar geometry occupies a large area, enhancing the possibility of surrounding residues approaching the ligand from all directions. In our previous studies on the inhibitory capabilities of various plant secondary metabolites,[4,33] we observed similar trends during protein docking analyses. Compounds such as cucurbitacin-B, momordicin-II, and charantadiol-A, which possess steroidal centers and various oxygen atoms, exhibit stronger inhibition potential compared to other molecules. The oxygen atoms within these structures facilitate the formation of hydrogen bonds, hence positively affecting binding affinity. Ligands featuring a wide tetracyclic core structure tend to be more effectively accommodated in protein binding sites compared to those lacking a tetracyclic core structure. Furthermore, these molecules showed promising selectivity. They inhibited the enzymes in target parasites without significantly affecting human homologs of the same enzyme or did so with lower affinity.

Previous studies have demonstrated the connection between the structural, electronic, topological, and vibrational properties of the synthesized 4-methylbenzylammonium nitrate (4MBN) and its non-covalent interactions using the combination of B3LYP/CC-PVTZ calculations and molecular docking techniques.[34] The results suggest that 4MBN exhibits biological activity and could serve as a potential inhibitor against schizophrenia.

To synthesize a pseudoeriocitrin-like molecule, one could propose a reaction where eriocitrin is oxidized (e.g., catalyzed by high temperature and metal), leading to bond formation between C3 and C8, resulting in a tetracyclic planar core structure. Given that pseudoeriocitrin may exist only briefly in a biological environment, various characterization techniques can confirm its existence and activity. In an experimental study by Gatfaoui *et al.*,[31] single crystals of a new proton transfer compound, phenylethylammonium trioxonitrate, were analyzed by solid-state XRD, thermal analysis, Infrared IR spectroscopy, and ionic conductivity to identify the chemical structure of the newly synthesized ligand. XRD revealed a slotted behavior of NO_3^- anions at the y = 1/4 and 3/4 positions, where 2-phenylethylammonium groups are linked by CeH/p interactions. The study evaluated the results from XRD analysis and MEP to obtain electron density maps of the ligand and accurately predicted its chemical structure and interactions.[35] If pseudoeriocitrin, the virtual compound examined in the present study, can be synthesized, it could be analyzed using XRD after crystallization. Its existence may also be investigated by HPLC without crystallization, and its structure analyzed using NMR.

4. Conclusion

Pseudoeriocitrin demonstrates a remarkable ability to inhibit various enzymes at extremely low concentrations without forming covalent bonds. Even if covalent bonds are formed, they only last for a short duration. Therefore, it is essential to continue this investigation to validate the efficacy and safety of pseudoeriocitrin. Further investigation

is needed to determine whether pseudoeriocitrin can be produced endogenously or through synthetic methods. This study offers novel insights into an inhibitor that exhibits exceptional efficacy at the femtomolar level. This discovery may be significant for understanding the structure-activity relationship of the most potent inhibitors in the future. Moreover, this study is the first to showcase the extraordinary inhibitory properties of a multi-radical molecule with a tetracyclic core structure through *in silico* analysis.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: Dilara Karaman
Formal analysis: Dilara Karaman
Investigation: Dilara Karaman
Methodology: Dilara Karaman
Writing – original draft: Dilara Karaman
Writing – review & editing: All authors

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Data supporting the findings are available on request from the corresponding author.

Further disclosure

(i) Part of or the entire set of findings have been presented at the 4th International Eurasia Scientific Researches and Innovation Congress, held on June 13–14, 2024 in Nakhchivan State University, Nakhchivan, Azerbaijan under the title "A New *in silico* Observation on a Virtual Molecule: Pseudoeriocitrin and Femtomolar Inhibition in Molecular Dockings."
(ii) The paper has been uploaded to or deposited in a preprint server: https://doi.org/10.32388/C446VT.2

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Appendix

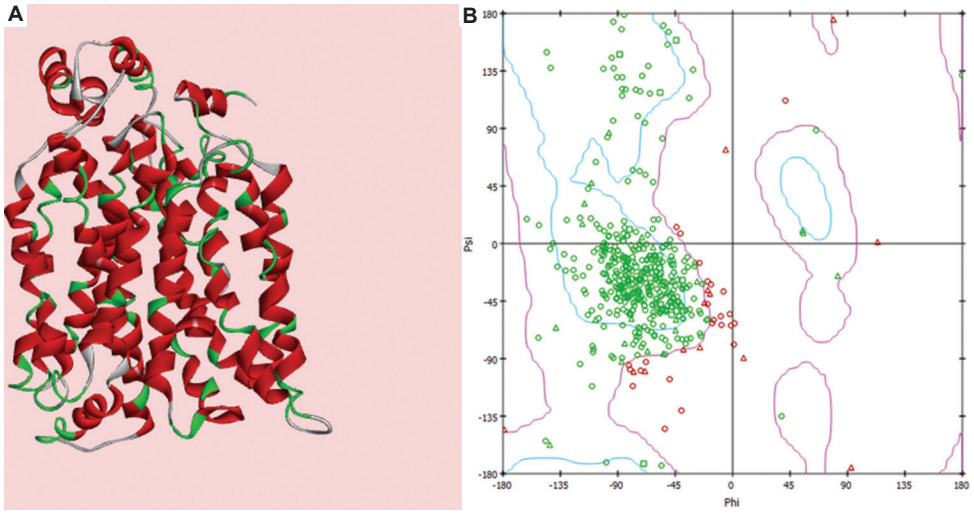

Figure A1. *Caenorhabditis elegans* glucose transporter 1 (CeGLUT1). (A) Homology model of CeGLUT1. (B) Ramachandran plot for CeGLUT1.

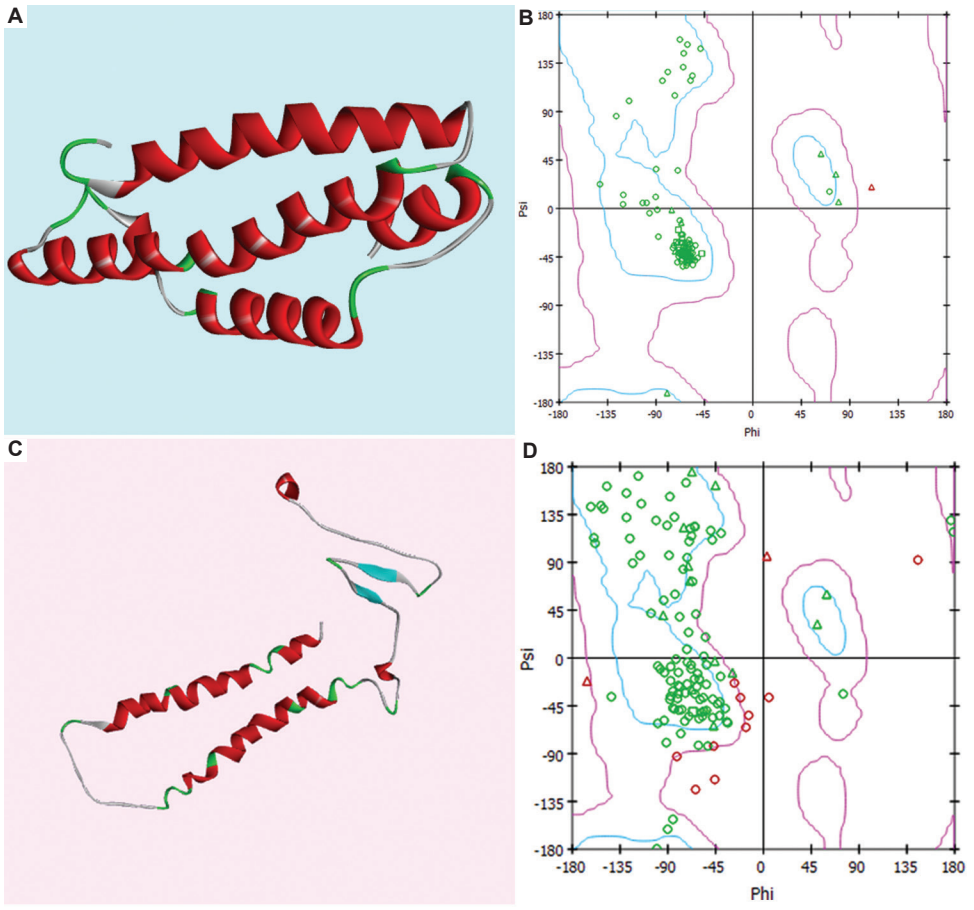

Figure A2. *Syphacia obvelata* cytochrome c oxidase 1 (SoCOX1) and SoCOX2. (A) Homology model of SoCOX1. (B) Ramachandran plot for SoCOX1. (C) Homology model of SoCOX2. (D) Ramachandran plot for SoCOX2.

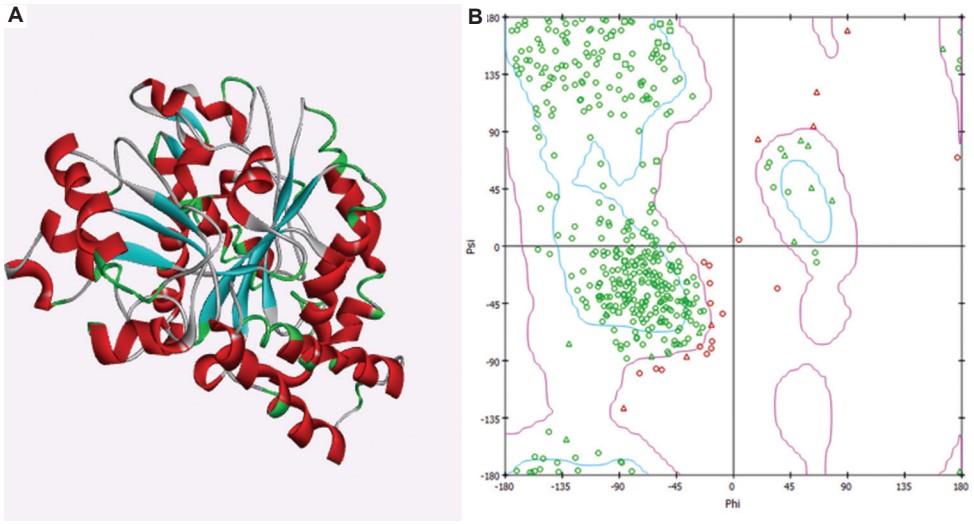

Figure A3. *Enterobius vermicularis* β-tubulin (EvTub). (A) Homology model of EvTub. (B) Ramachandran plot for EvTub.

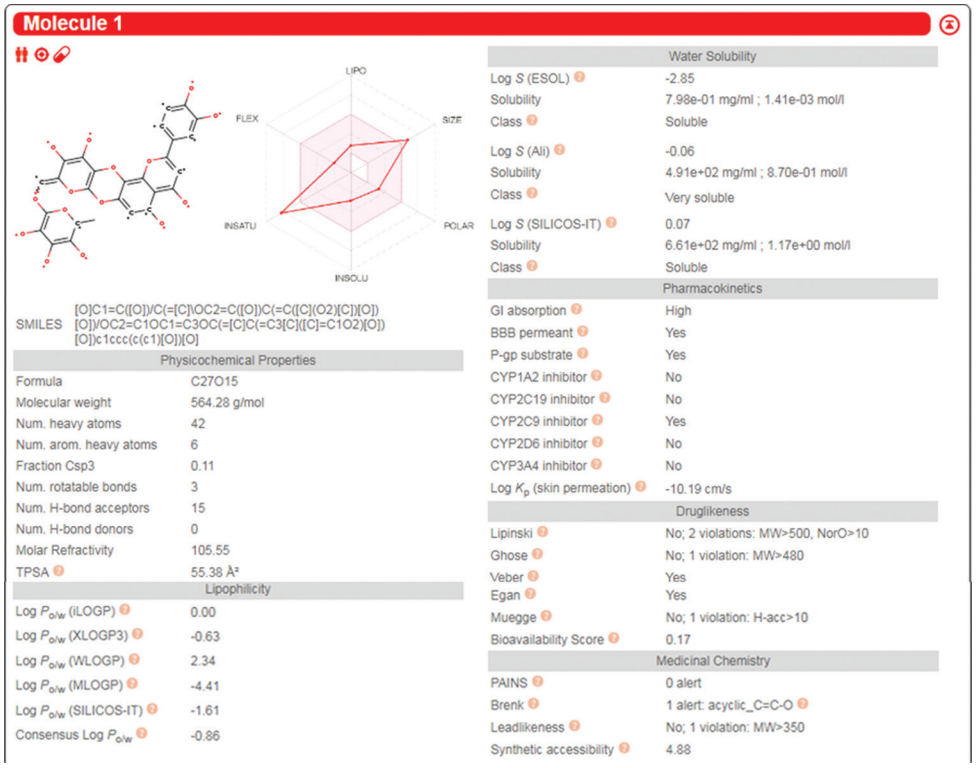

Figure A4. Swissabsorption, distribution, metabolism, and excretion result of pseudoeriocitrin

Video A1. The docking simulation of pseudoeriocitrin in the enzyme carnitine palmitoyl transferase 2 (PDB ID: 2FW3)

Video A2. The docking simulation of pseudoeriocitrin in the enzyme human fumarate reductase

Video A3. The docking simulation of pseudoeriocitrin in the enzyme Caenorhabditis elegans Glucose transporter 1

Video A4. The docking simulation of pseudoeriocitrin in the enzyme Syphacia obvelata cytochrome c oxidase 1

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ORIGINAL RESEARCH ARTICLE

Computational identification and molecular characterization of novel Aurora-B kinase inhibitors: Pharmacophore modeling, docking, and molecular dynamics simulations

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Abstract

Aurora-B, a serine-threonine kinase, plays a critical role in spindle assembly, chromosome alignment, mitotic checkpoint activation, and cytokinesis. The overexpression of Aurora-B leads to abnormal cell division, multinucleation, and centrosome amplification, contributing to cancer. To identify potential Aurora-B inhibitors, a 3D-quantitative structure-activity relationship study was conducted, leading to the selection of a five-feature pharmacophore model (AADRR) with optimal partial least square parameters for virtual screening. Molecular docking was performed to determine the binding interactions of the candidate ligands with the human Aurora-B: inner centromere protein complex (PDB ID: 4AF3), identifying LYS 106, ALA 157, GLU 161, and PHE 219 as key residues crucial for the enzyme inhibition. Based on virtual screening, pharmacokinetic properties, and docking analysis, five lead compounds were selected from the national cancer institute (NCI) database: Compound 1 (NCI ID: 695163), Compound 2 (NCI ID: 327359), Compound 3 (NCI ID: 721045), Compound 4 (NCI ID: 711797), and Compound 5 (NCI ID: 104546). To clarify the interactions between Aurora-B protein and lead compounds, molecular dynamics simulations were carried out. The results demonstrated strong interactions between the lead compounds and critical active-site residues such as ALA 157 and LYS 106. The active site interactions of the protein-ligand complex were further validated through molecular dynamics simulation studies, providing insights into their binding stability and inhibitory potential.

Keywords: Aurora-B kinase; Cytokinesis; 3D-quantitative structure-activity relationship; Molecular docking; Molecular dynamics simulations

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1. Introduction

The Aurora protein family of serine/threonine kinases plays key roles in mitosis, chromosome segregation, and cytokines.[1] During mitosis, the change in the organization of DNA due to incorrect segregation of chromosomes and dysregulation of cell cycle

checkpoints are the major characteristics of most tumor cells. Aurora kinases are highly expressed in mitotically active cells such as the spleen, thymus, testis, bone marrow, intestine, and fetal liver.[2] Homo sapiens express three Aurora kinase paralogues: Aurora-A, -B, and -C.[3-5] All three kinases show 67 – 76% sequence identity.[6,7] Aurora-A primarily localizes to spindle poles and centrosomes, and its disruption leads to centrosome separation and mitotic errors.[8,9] In contrast, Aurora-B, known as a chromosomal passenger protein, initially resides at chromosome centromeres during early mitosis and later shifts to microtubules during anaphase.[10,11] Aurora-B is essential for chromosome segregation, alignment, spindle-checkpoint function, and cytokinesis, interacting with partners such as inner centromere protein (INCENP), survivin, and borealin.[12] The precise function of Aurora-C in mammals remains unclear, but it is known to complement Aurora-B and aid cytokinesis.[13] Dysregulation of Aurora-A and -B is associated with various cancers, making Aurora-B a promising oncogene target.[14-19] Notable Aurora kinase inhibitors include Hesperadin, ZM447439, and VX680, with Hesperadin and VX680 inhibiting all three kinases.[20-22] ZM447439 selectively targets proliferating tumor cells during mitosis, sparing non-proliferating cells. VX680 exhibits promising results in arresting tumor cell proliferation *in vivo* and in animal models.

In the quest to discover novel scaffold inhibitors for a range of targets, various *in silico* approaches, including three-dimensional quantitative structure activity relationship (3D-QSAR), play a pivotal role.[23,24] For Aurora-B inhibition, a ligand-based pharmacophore model was employed to pinpoint the essential chemical features shared by effective inhibitors. To construct these hypotheses, a collection of known Aurora-B inhibitors was sourced from the Binding Database website (www.bindingdb.org/). The selection of the most robust pharmacophore hypothesis was based on rigorous statistical criteria, including the coefficient of determination (R^2), cross-validated correlation coefficient (Q^2), standard deviation (SD), variance ratio (F), and root mean square error (RMSE). This selected hypothesis was subsequently employed as a 3D query to initiate virtual screening. The screened compounds then underwent further refinement to ensure optimal pharmacokinetic properties, after which they were subjected to molecular docking studies to identify the best-fit molecules. The ultimate decision on lead compounds was made through a comprehensive comparison of docking analysis and pharmacokinetic properties. These chosen leads were then subjected to rigorous evaluation through molecular dynamics (MD) simulations to elucidate their binding mode interactions. The advanced *in silico* methods employed in this study, including rigorous statistical analysis, virtual screening, and MD simulations, provide valuable insights into the identification and optimization of Aurora-B inhibitors, thereby accelerating the drug discovery process.

2. Materials and methods

2.1. Protein preparation

Ligand-based pharmacophore modeling studies were carried out using the PHASE application implemented with Maestro (Phase, version 3.4, and Maestro, version 9.3, 2014, Schrödinger, LLC, New York, NY).[25,26] The 3D coordinates of the crystallographic structure of the human Aurora-B-INCENP complex (PDB ID: 4AF3) were downloaded from Brookhaven Protein Data Bank (www.rscb.com).[27] The protein complex was pre-processed and prepared using Protein Preparation Wizard in Maestro (Schrödinger software).[28] The minimization of the complex was continued using the Optimized Potential for Liquid Simulations (OPLS)–2005 force field until the root mean square deviation (RMSD) reached the value of 0.3 Å.[29] The preprocessing steps included the correction of heavy atoms, water molecules, cofactors, and metal ions, as well as the addition of missing hydrogen atoms, side chains, and protons. The Schrodinger suite's EPIK and IMPREF programs were employed for further refinement and minimization. To define the active site vicinity, the receptor grid generation module was utilized, creating a grid that encapsulated the ligand's surroundings. The resulting workspace configuration, appearing as a centroid in a cubic shape, precisely delineated the protein's active site. The molecular docking studies of hit molecules were conducted using Glide software (Glide, version 5.8, 2014, Schrödinger, LLC, New York, NY).[30] MD simulation studies were carried out using the DESMOND module (Desmond MD System, 2014, D.E. Shaw Research, version 3.1, and Maestro–Desmond Interoperability Tools, version 3.1, Schrödinger, New York, NY).[31]

2.2. Pharmacophore modeling

A total of 58 known inhibitors of Aurora-B with quantitative bioactivity data were used to design the pharmacophore model. The inhibitors were randomly divided into the training set and test set for structure-based pharmacophore generation and validation. Highly active and least active compounds were included in both training and test sets. The training set ligands provided critical information for pharmacophore design.

The pharmacophore modeling process consisted of five steps, as described in the following sections.

2.2.1. Ligand preparation

The 2D structures of compounds were imported into the Develop Common Pharmacophore Hypotheses (CPHs) panel. The structures were minimized and geometrically refined using the LIGPREP module, which neutralized the ionized structures to a pH 7 (neutral) and generated possible stereoisomers.[32,33] Conformers were generated using the rapid torsional angle search method (ConfGen) with distance-dependent dielectric solvation treatment and OPLS–2005 force field incorporated in PHASE. Molecular docking simulations were performed using an implicit solvent model with a distance-dependent dielectric (GB/SA) approach. The simulations employed a cutoff of 1 Å RMSD for interactions and consisted of 1000 iterations, with water as the implicit solvent. For each structure, a maximum of 1000 conformers were generated using 100 steps of pre-process minimizations and 50 steps of post-process minimizations. The maximum energy difference for a set of conformers of each molecule is 10 kcal/mol. The active and inactive ligands were assigned based on activity threshold values.

2.2.2. Creating pharmacophore sites

Pharmacophore features were defined to create sites for all ligands. PHASE provided six pharmacophore features: hydrogen bond acceptor (A), hydrogen bond donor (D), hydrophobic group (H), negatively ionizable (N), positively ionizable (P), and aromatic ring (R). All six features were utilized in pharmacophore site creation.

2.2.3. Finding common pharmacophore

Common pharmacophores were identified from the set of variants using a tree-based partition technique with a maximum depth of 5 and a minimum intersite distance of 2.0 Å. The initial and final box sizes were set to 32.0 Å and 1.0 Å, respectively, ensuring all active compounds were matched. CPHs were generated by varying the maximum and minimum number of sites and the number of matching active groups.

2.2.4. Scoring hypotheses

The generated CPHs were examined using the scoring procedure to find the best alignment of active molecules. The scoring process ranked hypotheses based on distinct features. The hypotheses table was used to choose the most appropriate hypothesis for further investigation.

2.2.5. Building QSAR model

For QSAR modeling, the dataset was divided into a training set (70%) and a test set (30%) based on the selected hypothesis. PHASE provides an atom-based and pharmacophore feature-based QSAR model. We used an atom-based QSAR model, in which the ligand structural components were represented by van der Waals atomic models. Atoms occupying the same region were categorized into six classes:

- Hydrogen-bond donors (D) – Atoms such as nitrogen, oxygen, phosphorus, and sulfur bonded to a hydrogen atom.
- Hydrophobic or nonpolar groups (H) – Carbon, hydrogen attached to carbon, and halogens.
- Negatively charged groups (N) – Atoms or functional groups carrying a formal negative charge.
- Positively charged groups (P) – Atoms or functional groups carrying a formal positive charge.
- Electron-withdrawing groups (W) – Atoms such as nitrogen and oxygen, including those that act as hydrogen-bond acceptors.
- Miscellaneous groups (X) – All other atoms and functional groups that do not fit into the above categories.

The partial least square (PLS) regression was carried out for QSAR modeling in PHASE, with a maximum of *N*/5 factors (where, *N* = number of ligands in the training set). The model's accuracy improved with an increasing number of PLS factors until overfitting was observed.[34,35] Three PLS factors were generated for all hypotheses with a grid spacing of 1 Å and the best model was selected based on statistical parameters, such as R^2, Q^2, SD, RMSE, F, Pearson R, and stability values for virtual screening.

2.3. Virtual screening

The validated hypothesis was used as a query to search for novel Aurora-B inhibitors. The National Cancer Institute (NCI) and Maybridge databases (https://dtp.cancer.gov/databases_tools/bulk_data.htm,https://www.thermofisher.in/chemicals/en/forms/maybridge-downloads.html) were explored to identify potential chemical structures. Hit molecules were further filtered based on *in silico* pharmacokinetic properties – absorption, distribution, metabolism, and excretion (ADME) – using the QIKPROP module, ensuring compliance with Lipinski's rule of five for drug-likeness.[36-38] The molecules with drug-likeness were subjected to molecular docking to find the best-fit interactions within the active site of the Aurora-B protein. The Glide software offers three distinct levels of docking methodologies: high throughput virtual screening (HTVS), standard precision (SP), and extra precision (XP). Initially, HTVS docking was employed to predict protein-ligand binding modes and rank ligands utilizing empirical scoring functions. The top-ranked ligands from HTVS underwent SP docking for further refinement. Finally, the most promising molecules were subjected to XP docking, which employs an anchor-and-grow algorithm

for high-precision binding mode refinement. Molecules were sequentially filtered using HTVS, followed by SP, and ultimately, top-ranked hits were selected for XP docking.[39] Lead molecules were selected based on Glide score rankings and pharmacokinetic properties.

2.4. MD simulation

Lead molecules with top-ranked Glide scores and acceptable pharmacokinetic properties were selected for MD simulation studies using the DESMOND module with OPLS-2005 force field. The protein-ligand complexes were solvated in an orthorhombic box using a predefined TIP3P water model.[40] The overall charge was neutralized by adding salt counter-ions. The simulations were performed under constant temperature (300 K) and pressure (1.01325 bar) conditions using the Nose-Hoover thermostat[41] and Martyna-Tobias-Klein barostat[42] methods. The simulations were performed using an NPT ensemble by considering the number of atoms, pressure, and timescale. During simulations, the long-range electrostatic interactions were calculated using the Particle-Mesh-Ewald method.[43,44]

3. Results and discussion

3.1. QSAR pharmacophore modeling

A dataset of 40 ligands was randomly selected for the training set and 18 ligands for the test set. The IC_{50} of the compound, defined by the concentration of the compound required to inhibit Aurora-B kinase activity by 50%, was computed. The chemical structure, along with their $-\log IC_{50}$ values, of the training and test set ligands are given in Table S1 and S2. The ligands with $-\log IC_{50}$ higher than 7.7 were considered "active," those lower than 6.5 as "inactive," and those with intermediate values as "moderately active" for the creation of CPHs. After ligand preparation, scoring hypotheses were evaluated by keeping the RMSD value below 1.2 Å and a vector score above 0.5. Using the tree-based partition technique, the pharmacophore identification resulted in 24 different variant hypotheses. The best hypothesis was selected based on the alignment of site points and vector alignment, volume overlap, selectivity, number of ligands matched, relative conformational energy, and activity. The hypothesis with five pharmacophoric – two hydrogen bond acceptors (A), one hydrogen bond donor (D), and two aromatic rings (R), denoted as AADRR – was identified as the best model based on R^2, SD, F, Q^2, RMSE, stability, and Pearson R values. The actual and predicted IC_{50} values for the training and test set molecules, along with their fitness scores, are presented in Table 1. The plot of actual versus predicted pIC_{50} ($-\log IC_{50}$) for both sets is shown in Figure 1.

According to Tropsha,[45] a high R^2 value is a necessary but not sufficient condition for a reliable QSAR model. This is further supported by RMSE and Pearson R values. Training set compounds were aligned in the AADRR pharmacophore model and analyzed using three PLS factors in PHASE. The QSAR results for AADRR yielded parameters indicating strong predictive capability (R^2 = 0.971, Q^2 = 0.907, Fit value = 403, and SD = 0.154). Therefore, the AADRR model was selected for QSAR analysis. The statistical parameters of AADRR are summarized in Table 2. The R^2 value (0.81) for the test set molecules confirms the model's predictive robustness. The spatial arrangement of the five-featured pharmacophore model, along with inter-feature distance, is shown in Figure 2.

3.2. Virtual screening

In this study, a total of 320,078 hit molecules were retrieved from two databases: the NCI database (265,242 compounds) and the Maybridge database (54,836 compounds). The initial screening process utilized "Pharmacophore Matching" using the AADRR model to select the top 1000 compounds. Subsequently, these compounds were further filtered using Lipinski's rule of five through the QIKPROP program, resulting in 822 promising compounds with favorable pharmacokinetic (ADME) properties. These 822 compounds were then subjected to a comprehensive docking analysis using HTVS, SP, and XP molecular docking.

To identify key active site residues, known Aurora-B inhibitors – Hesperadin, ZM447439, and VX-680 – were initially docked with the human Aurora-B: INCENP complex. The results revealed ALA 157 and LYS 106 as important residues for successful binding (Figure S1). The Lipinski's rule-compliant molecules (N = 822) were subjected to rapid screening by HTVS, after which the top-ranked compounds were selected for SP docking. Further, the first 58 compounds were selected after XP docking. The virtual screening workflow is presented in Figure 3. Final lead selection from the 58 XP-docked hits was based on Glide docking scores, binding interactions, and pharmacokinetic properties. Five lead compounds were identified from the NCI database: NCI ID 695163 (compound 1), 327359 (compound 2), 721045 (compound 3), 711797 (compound 4), and 104546 (compound 5). The chemical structures of these compounds and the known inhibitors are presented in Figure 4.

The primary criterion for the selection of the final five lead compounds was the binding affinity, with higher Glide docking scores indicating stronger interactions with the Aurora-B active site. The identified interactions between the Aurora-B protein and the lead compounds are shown in Figure 5. The binding interactions of the compounds

Table 1. The fitness and activity data of training and test set molecules

Ligand no.	Set type	$-\log IC_{50}$	Predicted activity for PLS Factor 3	Residuals	Fitness
1	Training	9.398	9.31	−0.088	0.99
2	Training	9.301	9.21	−0.091	1.04
3	Test	9.222	9.19	−0.032	1.02
4	Training	9.155	9.19	0.035	1.05
5	Test	9.097	9.18	0.083	1.06
6	Training	9.000	9.17	0.170	1.05
7	Training	8.022	8.01	−0.012	2.68
8	Training	7.971	7.82	−0.151	1.57
9	Test	7.959	7.62	−0.339	2.66
10	Test	7.886	7.89	0.004	1.64
11	Test	7.854	7.36	−0.494	2.12
12	Test	7.810	7.35	−0.460	1.21
13	Test	7.770	7.62	−0.150	0.93
14	Training	7.745	7.69	−0.055	2.2
15	Training	7.721	7.78	0.059	1.29
16	Test	7.703	7.70	−0.003	3
17	Training	7.699	7.69	−0.009	2.61
18	Training	7.678	7.61	−0.068	1.68
19	Training	7.635	7.66	0.025	1.28
20	Training	7.602	7.64	0.038	2.65
21	Training	7.600	7.65	0.050	1.76
22	Training	7.592	7.64	0.048	1.44
23	Training	7.523	7.53	0.007	1.19
24	Training	7.394	7.36	−0.034	1.61
25	Training	7.364	7.33	−0.034	1.71
26	Training	7.299	7.35	0.051	1.51
27	Test	7.300	7.17	−0.130	1.45
28	Training	7.276	7.19	−0.086	1.03
29	Test	7.247	7.20	−0.047	1.64
30	Training	7.102	7.10	−0.002	1.12
31	Training	7.077	7.12	0.043	1.46
32	Training	7.036	7.07	0.034	1.52
33	Training	7.027	7.07	0.043	1.48
34	Test	7.004	6.54	−0.464	1.22
35	Training	6.975	6.99	0.015	1.05
36	Test	6.910	6.97	0.060	1.02
37	Training	6.857	6.71	−0.147	1.26
38	Training	6.842	6.85	0.008	1.61
39	Test	6.800	6.90	0.100	1.34
40	Training	6.796	6.81	0.014	1
41	Test	6.759	7.13	0.371	1.62
42	Training	6.745	6.88	0.135	1.54
43	Training	6.719	6.67	−0.049	2.19
44	Training	6.712	6.67	−0.042	1.81
45	Training	6.699	6.78	0.081	1.18
46	Training	6.678	6.64	−0.038	1.2
47	Test	6.646	6.97	0.324	1.4
48	Training	6.636	6.64	0.004	1.25
49	Test	6.635	6.93	0.295	1.39
50	Test	6.600	7.03	0.43	1.22
51	Training	6.400	6.42	0.02	0.49
52	Training	6.312	6.16	−0.152	1.76
53	Test	6.232	6.14	−0.092	1.76
54	Training	6.111	6.18	0.069	1.78
55	Training	6.107	6.18	0.073	1.74
56	Training	6.013	6.12	0.107	1.71
57	Training	6.000	5.96	−0.04	1.08
58	Training	5.900	5.91	0.01	0.95

(Cont'd...)

Table 1. ***(Continued)***

Note: $-\log IC_{50}$ were computed with the IC_{50} in μM. Predicted activity for PLS Factor 3 represents the predicted biological activity of the ligand, based on the third principal latent variable (Factor 3) in the PLS regression model. Residuals are the difference between the observed and predicted values of activity, indicating the model's prediction error. Fitness is a scoring function that represents how well the ligand fits the model, with higher values generally indicating a better fit.

with critical amino acid residues of Aurora-B, such as ALA 157, LYS 106, GLU 161, and PHE 219, were carefully analyzed (Figure S2). Only compounds demonstrating strong interactions with these critical residues, as well as favorable ADME properties and compliance with Lipinski's rule of five, were considered for further analysis. To ensure structural diversity, the final leads represented different chemical scaffolds, offering a range of molecular architectures with the potential to yield novel inhibitors. The conformational stability of the selected compounds was further validated through MD simulations, confirming stable binding interactions without significant structural deviations. This multi-parameter selection process ensured that the final five compounds exhibited potent inhibitory activity, desirable pharmacokinetic properties, and structural novelty, making them promising candidates for further exploration.

3.3. Pharmacokinetic properties and drug-likeness evaluation

A comparative analysis of the pharmacokinetic properties of the five lead compounds from the NCI database and the

Table 2. Statistical parameters of the best AADRR model

Hypothesis ID	PLS Factor	SD	R^2	F	P	Stability	RMSE	Q^2	Pearson R
AADRR.94	1	0.3668	0.8284	183.5	3.999 e-16	0.9384	0.357	0.804	0.8989
	2	0.2337	0.9322	254.3	2.389 e-22	0.8595	0.2609	0.8953	0.9463
	3	0.1547	0.9711	403	9.626 e-28	0.7662	0.245	0.9077	0.9529

Notes: PLS: Partial least square; SD: Standard deviation of the regression; R^2: Coefficient of determination; F: Variance ratio; P: Significance level of the variance ratio; RMSE: Root mean square error; Q^2: Cross-validated correlation coefficient; Pearson R: correlation between predicted and observed activity for test set.

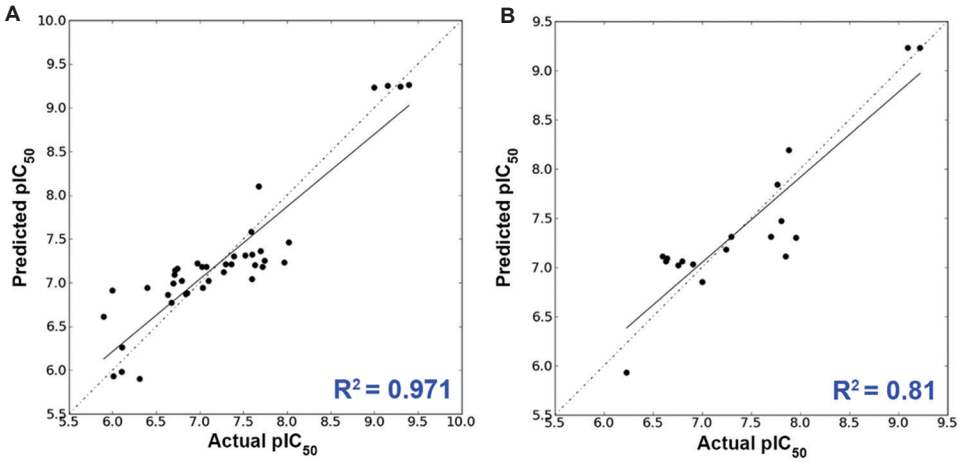

Figure 1. The correlation of actual versus predicted IC_{50} (pIC_{50}) values for the training set (A) and test set (B) ligands. pIC_{50} is the negative logarithm of IC_{50} ($-logIC_{50}$), representing ligand potency. The R^2 value indicates the predictive accuracy of the QSAR model for each set.

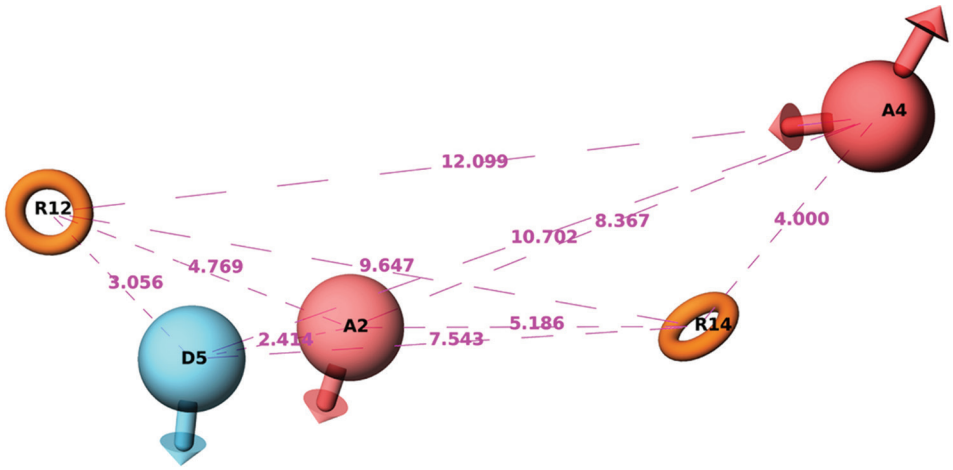

Figure 2. (A) The spatial arrangement of the AADRR model with two hydrogen-bond acceptors, (D) one hydrogen-bond donor, and (R) two aromatic rings. (Å) The numbers in pink represent the distances between atoms or functional groups, measured in angstroms.

three known Aurora-B kinase inhibitors – Hesperadin, VX680, and ZM447439 – was conducted to assess their drug-likeness based on Lipinski's rule of five and other pharmacokinetic parameters (Table 3). Lipinski's rule of five states that an ideal drug candidate should have a molecular weight of <500, fewer than 5 hydrogen bond donors, fewer than 10 hydrogen bond acceptors, and a partition coefficient (log P) below 5. While Hesperadin (513 g/moL) and VX680 (516 g/moL) slightly exceed the threshold, ZM447439 – with a molecular weight of 464 g/moL – complies with all criteria. The five lead compounds exhibit molecular weights well below 500 g/moL, ranging from

278.31 g/moL to 447.83 g/moL, ensuring zero violations of Lipinski's rule.

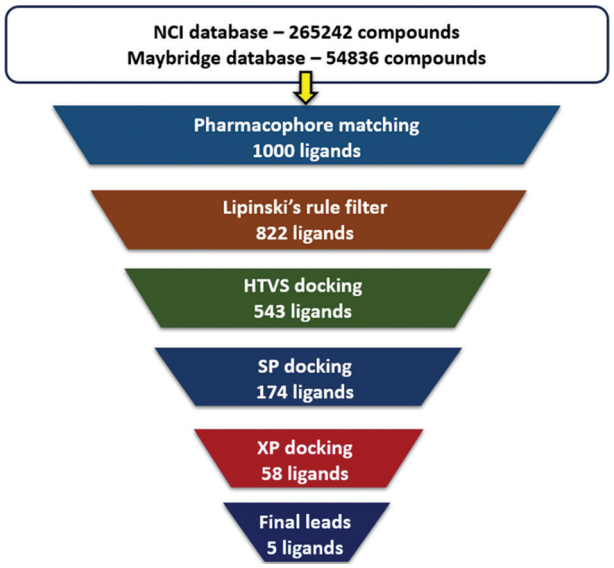

Figure 3. The virtual screening workflow. Through these screening methods, five lead compounds were identified from the binding database and used for further analysis.
Abbreviations: HTVS: High throughput virtual screening; NCI: National Cancer Institute; SP: Standard precision; XP: Extra precision.

The number of hydrogen bond donors and acceptors also plays a crucial role in drug permeability and solubility. The hydrogen bond donor counts of Hesperadin (2), VX680 (2), and ZM447439 (3) are within the acceptable range. All of the lead compounds exhibited similar donor counts, ranging between 1 and 3, further confirming their compliance with drug-likeness criteria. For hydrogen bond acceptors, the known inhibitors exhibit values of 8.5 – 10.2, with Hesperadin slightly exceeding the threshold; in comparison, the lead compounds showed values of 4.25 – 8.45, all falling within the acceptable range. Lipophilicity assessed through log P influences membrane permeability; the known inhibitors exhibit values of 3.793 – 4.492, all within the acceptable range (<5); the identified lead compounds exhibited values of 1.554 – 3.148, suggesting favorable lipophilicity while maintaining optimal solubility and permeability.

Oral absorption is a key determinant of bioavailability and an absorption percentage >80% is considered ideal. ZM447439 shows complete absorption (100%), while VX680 and Hesperadin exhibit 78.4% and 86.5%, respectively. Among the lead compounds, all exhibited high absorption percentages, with values of 84.4 – 100%, indicating excellent oral bioavailability. Aqueous solubility (S, mol/L) is another crucial parameter, with an optimal

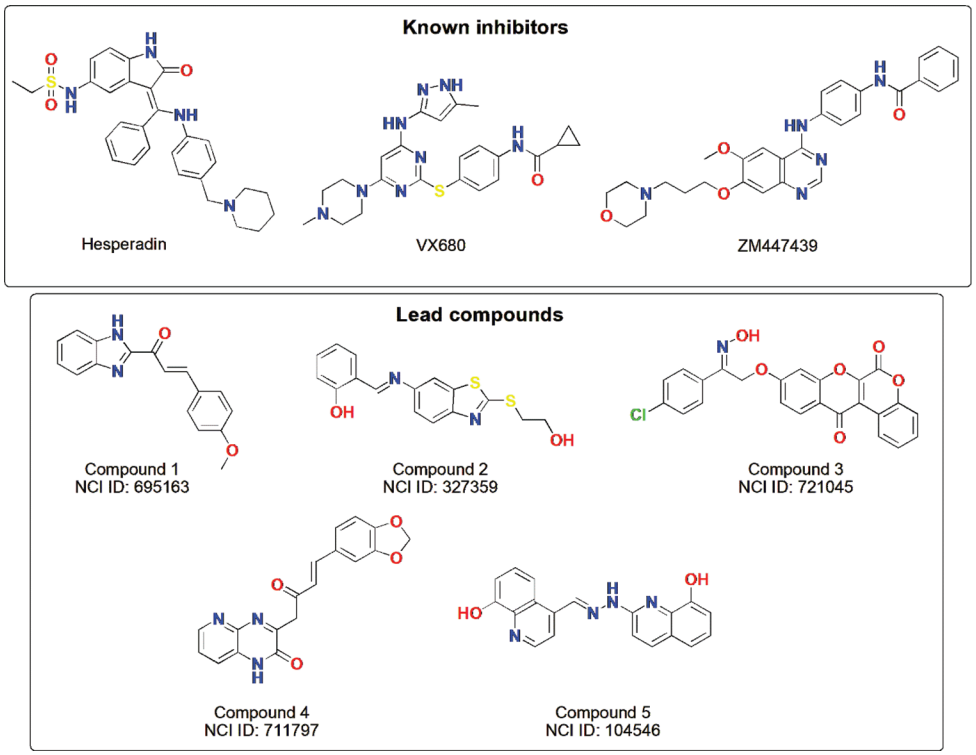

Figure 4. The chemical structures of the known Aurora-B kinase inhibitors and the five lead compounds identified from NCI database as potent inhibitors
Abbreviation: NCI: National cancer institute.

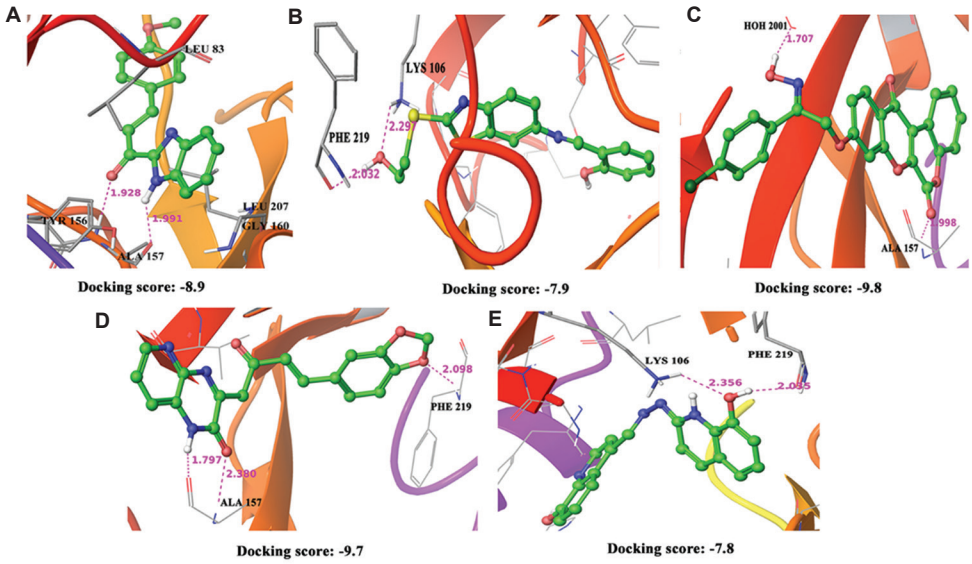

Figure 5. Docking poses of Aurora-B protein (PDB ID: 4AF3) with lead compounds. The docking results for (A) compound 1, (B) compound 2, (C) compound 3, (D) compound 4, and (E) compound 5 are shown. The numbers in pink represent the distances between atoms or functional groups in angstroms (Å), indicating the spatial relationships within the binding site. The black text represents the three-letter codes for the amino acids present in the binding site of the protein. Additionally, the amino acids are labeled with specific residue numbers (e.g., PHE219), where "PHE" denotes the amino acid (phenylalanine) and "219" indicates its position in the protein sequence. Molecular docking studies were carried out using the Glide module of Schrodinger software. The 4AF3 structure was downloaded from the Protein Data Bank (https://www.rcsb.org/) and the lead compound structures were sourced from the Binding Database (http://www.bindingdb.org).

Table 3. The pharmacokinetic properties of the lead compounds and the known Aurora-B kinase inhibitors

No.	Drug-like parameters	Lead compound (NCI ID)					Known inhibitors		
		1 (695163)	2 (327359)	3 (721045)	4 (711797)	5 (104546)	Hesperadin	VX680	ZM447439
1	MW[a]	278.31	330.419	447.831	335.318	330.345	513.595	516.657	464.587
2	Donor HB[b]	1	2	1	1	3	2	2	3
3	Accpt HB[c]	4.25	4.95	8.45	8	5.5	10.2	9	8.5
4	QPlogPo/w[d]	3.148	3.132	3.005	1.554	2.338	4.492	4.363	3.793
5	Rule of five[e]	0	0	0	0	0	1	1	0
6	Human oral absorption (%)[f]	100	96.956	89.088	84.471	84.442	86.524	78.484	100
7	QPlogS[g]	−4.055	−4.125	−4.928	−2.975	−3.97	−6.098	−5.865	−5.898
8	QPlogHERH[h]	−5.971	−5.916	−6.663	−5.473	−6.083	−8.718	−7.676	−7.077
9	QPlogBB[i]	−0.56	−0.909	−1.26	−1.012	−1.298	−0.695	−1.407	−0.844

Notes: Parameters (with their ideal values): [a]Molecular weight of the compound in g/mol (<500); [b]Number of hydrogen bond donor (<5); [c]Number of hydrogen bond acceptor (<10); [d]Partition coefficient value between octanol and water (<5); [e]Number of violations for Lipinski's rule; [f]Percentage of human oral absorption (>80: high, <25: poor); [g]Predicted aqueous solubility in mol/L (between−6.5 and 0.5); [h]Predicted IC_{50} value for blockage of HERG K+channels in μM (<−5); [i]Predicted blood-brain barrier permeability, (between−3 and 1.2).

range between −6.5 to 0.5 to ensure sufficient solubility for systemic circulation; the known inhibitors have solubility values of −6.098, −5.865, and −5.898, respectively, whereas the lead compounds showed better solubility, ranging from -2.975 to -4.928, making them more favorable for drug formulation.

The predicted IC_{50} values for Human Ether-à-go-go-Related Gene Potassium (HERG K+) channel blockage assess cardiotoxicity risks, with lower (more negative) values indicating higher risks. Hesperadin (−8.718), VX680 (−7.676), and ZM447439 (−7.077) exhibit strong inhibition, raising safety concerns. In contrast, the lead compounds show reduced HERG inhibition (−5.473 to −6.663), suggesting lower cardiotoxic risk. Blood-brain barrier (BBB) permeability, critical for central nervous system (CNS) penetration, is optimal within the range of −3 to 1.2;

the values for the known inhibitors range from −0.695 to −1.407, suggesting moderate BBB permeability; the lead compounds show comparable values between −0.56 and −1.298, indicating their potential CNS activity for therapeutic applications. Overall, the pharmacokinetic evaluation reveals that all five lead compounds exhibit favorable drug-likeness properties with no violations of Lipinski's rule. Their optimal molecular weights, hydrogen bonding characteristics, log *P* values, high absorption rates, superior solubility, reduced cardiotoxicity risks, and comparable BBB permeability suggest superior pharmacokinetic profiles compared to the known inhibitors, reinforcing their potential as promising Aurora-B kinase inhibitors.

3.4. MD simulations

MD simulations were conducted to evaluate the stability, flexibility, and binding interactions of the five lead compounds within the active site of Aurora-B kinase over a 100 ns simulation period. RMSD analysis was employed to assess the conformational stability of the protein-ligand complexes by monitoring backbone deviations over time. The RMSD plots of all five lead compounds are shown in Figure 6. Initially, all complexes exhibited fluctuations as they adapted to the thermal conditions of the system, followed by stabilization as the simulation progressed. Among the five compounds, compound 5 demonstrated superior stability, maintaining a consistent RMSD profile beyond 20 ns and remaining stable throughout the entire simulation. In contrast, compounds 2 and 4 exhibited pronounced fluctuations around 50 ns, persisting for approximately 10 – 15 ns before stabilizing. While compounds 1 and 3 showed minimal fluctuations, indicating strong binding affinity and structural integrity, compound 4 displayed transient instability before attaining a stable conformation by the end of the 100 ns simulation period. To further elucidate the binding mechanisms at the atomic level, various intermolecular interactions such as hydrogen bonding, hydrophobic contacts, ionic interactions, salt bridges, and π-π stacking were extensively analyzed. These interactions play a fundamental role in determining ligand affinity and stability within the binding pocket. Hydrogen bonding was identified as a key stabilizing factor, with multiple direct and water-mediated hydrogen bonds contributing to the persistence of the protein-ligand complexes. In addition, π-π stacking and π-cation interactions provided additional stabilization by facilitating optimal ligand orientation within the active site. Water bridge interactions highlighted the role of solvent molecules in mediating ligand-protein interactions, further enhancing stability. The post-simulation protein-ligand interactions are depicted in Figure 7.

The detailed molecular interactions revealed that compound 1 primarily formed hydrogen bonds with LYS 106 and ALA 157, while ASN 205 and GLU 204 contributed to water bridge formation, indicating a well-stabilized binding mode. Compound 2 exhibited hydrogen bonding with GLU 161 and LYS 106, suggesting a stable interaction network within the binding site. Similarly, compound 3 established hydrogen bonds with ALA 157, while GLU 161 and LEU 83 participated in water bridge formation, reinforcing

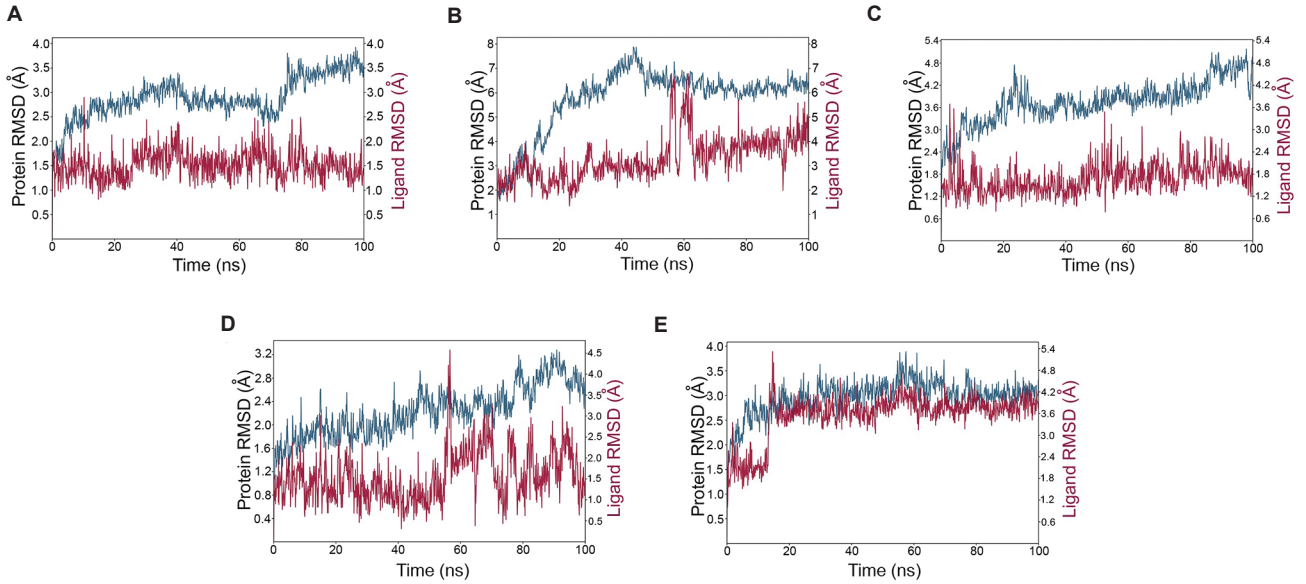

Figure 6. RMSD of Aurora-B protein-ligand complex for (A) compound 1, (B) compound 2, (C) compound 3, (D) compound 4, and (E) compound 5. The RMSD of the protein and ligand after the initial RMSD values were stabilized. The RMSD values for the protein are presented on the left Y-axis and that of the ligand are indicated on the right Y-axis. The Cα RMSD graph is shown in blue, whereas the ligand fit on the protein is shown in red.
Abbreviation: RMSD: Root mean square deviation.

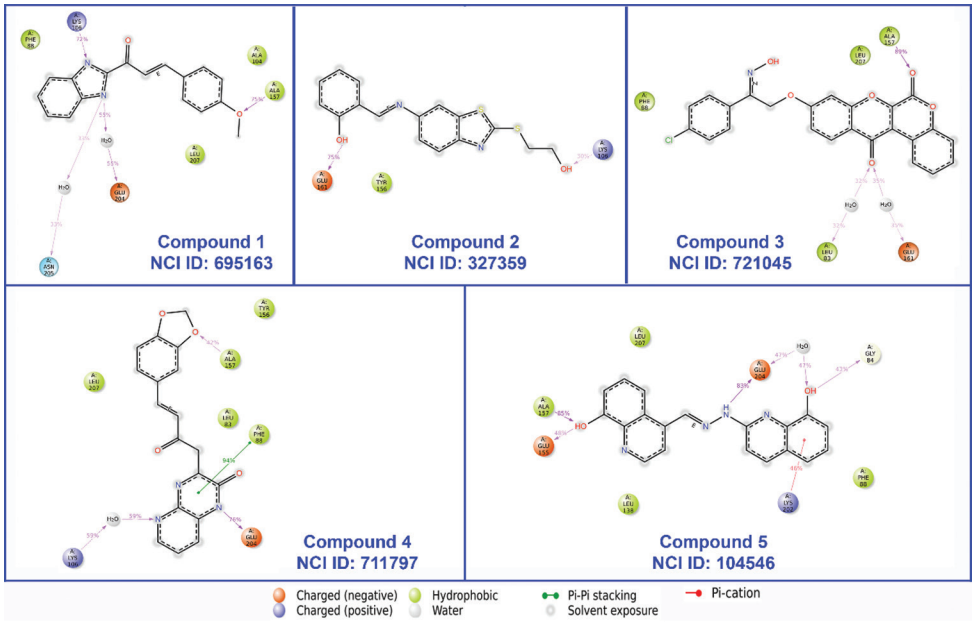

Figure 7. The 2D view of protein-ligand interactions after MD simulations for the five lead compounds identified from NCI database as potent Aurora-B inhibitors
Abbreviations: MD: Molecular dynamics; NCI: National Cancer Institute.

its structural stability. Compound 4 displayed a complex interaction profile, forming hydrogen bonds with ALA 157 and GLU 204, π-π stacking interactions with PHE 88, and a crucial water bridge interaction with LYS 106, indicating an extensive network of stabilizing forces. Compound 5, which exhibited the most favorable stability profile, demonstrated strong hydrogen bonding interactions with ALA 157, GLU 155, GLU 204, and GLY 84, while LYS 202 contributed to additional stabilization through π-cation interactions. A comparative analysis of molecular docking and MD simulation results revealed a strong correlation between the residues involved in binding interactions. Key residues, such as ALA 157, LYS 106, and PHE 219, identified in docking studies, were also observed in MD simulations, reinforcing the accuracy of docking-based predictions. The comparison of protein-ligand interactions in molecular docking and MD simulations is provided in Table 4. Furthermore, statistical analysis using histograms provided deeper insights into the frequency and distribution of intermolecular interactions, including hydrogen bonding, hydrophobic interactions, ionic interactions, and water bridge formations (Figure 8). The presence of consistent hydrogen bonding interactions throughout the simulation period underscores their critical role in ligand stability and affinity.

3.5. Structural comparison and structure-activity relationship (SAR) analysis

A comparative structural analysis of the identified lead compounds and the established Aurora-B kinase inhibitors – Hesperadin, VX680, and ZM447439 – revealed crucial pharmacophoric similarities supporting their potential as effective inhibitors. Several lead compounds exhibit conserved core scaffolds and functional groups known to facilitate kinase inhibition, reinforcing their relevance as promising candidates for further development. Compounds 1, 2, and 4 contain bicyclic heterocyclic systems such as benzimidazole, benzothiazole, and benzodioxole, which structurally resemble the indole core of Hesperadin. These bicyclic moieties are well-documented for stabilizing kinase-inhibitor interactions through hydrogen bonding and π – π stacking within the ATP-binding pocket.[46] Compound 5 and compound 4 feature quinoline and pyrido-pyrazine frameworks, respectively, which are analogous to the quinazoline core of ZM447439, suggesting similar binding orientations and inhibitory potential. In addition to core scaffolds, specific functional groups within the lead compounds further enhance their potential for kinase inhibition. Sulfur and nitrogen heteroatoms, which play a key role in modulating electronic properties and molecular interactions, are present in both Hesperadin and VX680. Notably, compound 2 contains these heteroatoms, enhancing its ability to form critical hydrogen bonds and coordination interactions with Aurora-B active site residues. The amide functional group, a known pharmacophoric feature associated with enhanced binding affinity and molecular stability, is present in compound 4, aligning with its presence in all three reference inhibitors. In addition, the

Table 4. The key residues of protein-ligand interactions identified for the lead compounds in molecular docking study and MD simulations

Lead compound (NCI ID)	IUPAC name	Molecular docking	MD simulations
1 (695163)	(E)-1-(1H-benzo[d] imidazol-2-yl)-3-(4-methoxyphenyl) prop-2-en-1-one	ALA 157	LYS106, ALA157, ASN205, GLU204
2 (327359)	(E)-2-(((2-((2-hydroxyethyl) thio) benzo[d] thiazol-6-yl) imino) methyl) phenol	LYS106, PHE219	GLU161, LYS106
3 (721045)	(E)-9-(2-(4-chlorophenyl)-2-(hydroxyimino) ethoxy) chromeno[3,4-b] chromene-6,12-dione	ALA157	ALA157, GLU161, LEU83
4 (711797)	(E)-3-(4-(benzo[d][1,3]dioxol-5-yl)-2-oxobut-3-en-1-yl) pyrido[2,3-b] pyrazin-2 (1H)-one	ALA157, PHE219, LYS106.	ALA157, PHE88, GLU204, LYS106
5 (104546)	4-((E)-((E)-(8-hydroxyquinolin-2 (1H)-ylidene) hydrazono) methyl) quinolin-8-ol	LYS106, PHE219, PHE88.	ALA157, GLU155, GLU204, GLY84, LYS202

Abbreviation: MD: Molecular dynamics.

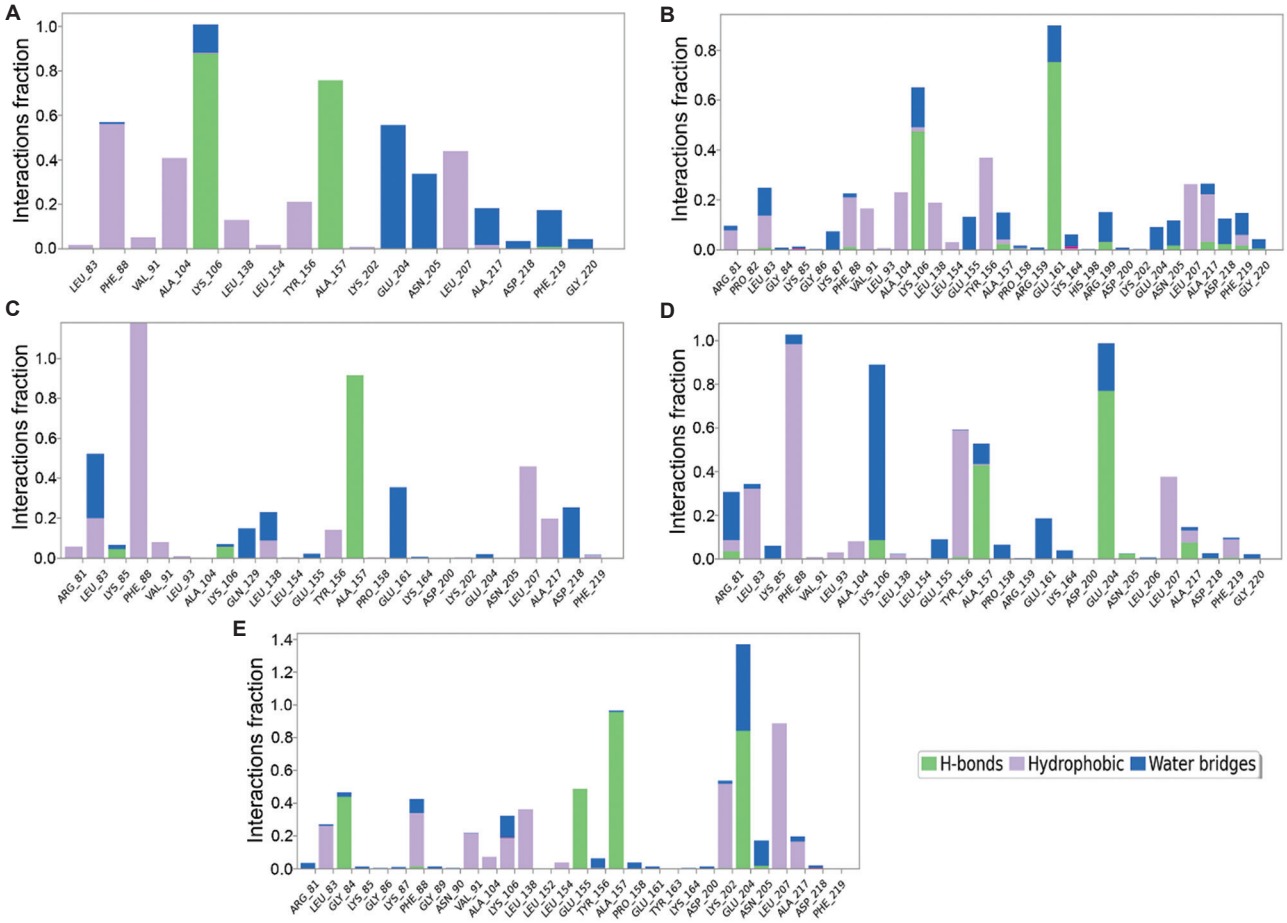

Figure 8. The histogram representation of protein-ligand interactions after molecular dynamics (MD) simulations for (A) compound 1, (B) compound 2, (C) compound 3, (D) compound 4, and (E) compound 5

carbonyl functional group, which contributes to ligand-target interactions through hydrogen bonding, is observed in compounds 1, 3, and 4, as well as in all three known inhibitors, further supporting their structural congruence. These shared motifs, including bicyclic heterocycles, amide linkages, and carbonyl functionalities, provide a strong rationale for the selection of the lead compounds as potential Aurora-B kinase inhibitors.

A detailed SAR analysis was performed to evaluate how specific molecular features influence the binding affinity and inhibitory potential of the lead compounds. Effective kinase inhibitors rely on key pharmacophoric features facilitating interactions with the active site of the Aurora-B kinase protein. These features include hydrogen bond donors and acceptors, hydrophobic regions, aromatic rings, charged functional groups, and other functional moieties – such as benzimidazole, benzothiazole, and benzodioxole. The molecular docking and MD simulations provided insights into these interactions, revealing that hydrogen bond formation plays a crucial role in stabilizing the protein-ligand complex. The lead compounds demonstrated varying degrees of hydrogen bonding with key amino acid residues, such as ALA 157, LYS 106, and PHE 219, reinforcing their role in kinase inhibition. Furthermore, π-π stacking and hydrophobic interactions observed in multiple lead compounds suggest that aromatic moieties are essential for improving binding affinity. Electrostatic interactions, particularly those involving nitrogen and sulfur-containing functional groups, contributed significantly to the stability of some lead compounds, mirroring similar interaction patterns observed in known Aurora-B inhibitors. Water bridge interactions further supported the stabilization of the complexes, emphasizing the role of solvent-mediated interactions in ligand binding. MD simulations confirmed the dynamic behavior of the lead compounds, with RMSD plots indicating stable conformations within the binding pocket. Collectively, the structural comparison and SAR analysis suggest that the identified lead compounds exhibit key pharmacophoric features essential for Aurora-B kinase inhibition. Their resemblance to known inhibitors, both in core scaffold architecture and functional group distribution, strongly supports their potential as promising drug candidates.

4. Conclusion

Our findings suggest that the AADRR pharmacophore model, docking studies, and MD simulations provide valuable structural insights for Aurora-B kinase inhibition. Notably, previous studies identified interactions between specific residues (LEU 83, PHE 88, VAL 91, ALA 157, and GLU 155) within the Aurora-B binding pocket, leading to the development of a pharmacophoric model with seven distinct features, including two hydrophobic elements, one donor, one acceptor, and three exclusion volumes.[47] However, our study introduced a five-feature pharmacophoric model (AADRR), which exhibited superior predictive parameters based on PLS analysis. This approach led to the identification of five promising lead compounds from a screening pool of 320,000 compounds sourced from the Maybridge and NCI databases. These lead compounds showed interactions with the Aurora-B binding pocket, underscoring their potential for further exploration. Specifically, we found that LYS 106, ALA 157, GLU 161, and PHE 219 play pivotal roles in ligand binding, highlighting these residues as key targets for future Aurora-B inhibitor development.

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Conflict of interest

The authors declare that they have no competing interests.

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Ethics approval and consent to participate

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Consent for publication

Not applicable.

Availability of data

Data are available from the corresponding author on reasonable request.

Further disclosure

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CASE REPORT

Severe Vitamin D deficiency as a potential contributor to cherry angiomas: A case study and novel hypothesis

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Abstract

Cherry angiomas are common benign vascular lesions with a poorly understood underlying pathogenesis. While factors such as aging, hormonal changes, and oxidative stress have been implicated, this case introduces a novel hypothesis linking severe Vitamin D deficiency to the development of cherry angiomas. We report the case of a 27-year-old Arab female with no medical, genetic, or familial predisposition to cherry angiomas. The patient presented with multiple asymptomatic, erythematous, dome-shaped lesions localized to the breast and neck regions. Comprehensive laboratory evaluations were unremarkable except for severe Vitamin D deficiency, with a serum level of 3 ng/mL (normal: 30 – 100 ng/mL). Vitamin D deficiency is known to disrupt endothelial function, increase oxidative stress, and upregulate pro-angiogenic mediators such as vascular endothelial growth factor. These molecular disturbances may promote capillary proliferation and vascular instability, providing a plausible mechanism for the sudden onset of cherry angiomas in this patient. This case highlights the importance of Vitamin D in vascular health and proposes a potential link between its deficiency and the pathogenesis of cherry angiomas. Further research is warranted to explore this relationship and elucidate the underlying molecular mechanisms, which may offer new insights into the prevention and management of cherry angiomas in patients with Vitamin D deficiency.

Keywords: Cherry angiomas; Vitamin D deficiency; Angiogenesis; Endothelial dysfunction; Dermatology

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1. Background

Cherry angiomas are common benign vascular skin lesions characterized by clusters of dilated capillaries that form red, dome-shaped papules. Furthermore, referred to as senile angiomas due to their increasing prevalence with age, they can occur at any stage of life. Histologically, cherry angiomas result from capillary proliferation in the upper dermis, producing their characteristic erythematous appearance.[1] While the exact pathophysiology of cherry angiomas remains incompletely understood, it is hypothesized that hormonal changes, genetic predisposition, oxidative stress, and vascular aging play significant roles. From a clinical perspective, cherry angiomas are typically asymptomatic and do not require intervention. However, therapeutic options such as laser therapy, cryotherapy, electrocauterization, or excision may be considered

for lesions that are numerous, rapidly proliferating, or cosmetically concerning. Despite their benign nature, sudden eruptions of cherry angiomas have been linked to various systemic conditions, underscoring the need for a deeper understanding of their pathogenesis and potential triggers.[2]

Vitamin D, a fat-soluble secosteroid, plays a pivotal role in calcium homeostasis, bone metabolism, and immune regulation. Beyond these traditional roles, Vitamin D exerts broad effects on cellular growth, differentiation, and angiogenesis.[3] Deficiency in Vitamin D, particularly in its severe forms, has been implicated in a range of dermatological conditions, including psoriasis, eczema, and delayed wound healing. At a molecular level, Vitamin D regulates gene expression through its active form, 1,25-dihydroxyvitamin D (calcitriol), which binds to the Vitamin D receptor (VDR) expressed in various tissues, including the skin.[4] Through VDR signaling, Vitamin D modulates pathways that regulate inflammation, immune responses, and endothelial function. Given the established link between Vitamin D and vascular health, it is plausible to hypothesize that severe Vitamin D deficiency could contribute to the development of cherry angiomas.[5] One proposed mechanism involves endothelial dysfunction and increased oxidative stress resulting from impaired VDR signaling. Vitamin D deficiency may disrupt angiogenesis, leading to excessive capillary proliferation and structural changes in dermal blood vessels. On a molecular level, Vitamin D is known to inhibit pro-angiogenic factors such as vascular endothelial growth factor (VEGF).[6] In the context of Vitamin D deficiency, upregulation of VEGF and other angiogenic mediators may promote capillary dilation and proliferation, leading to the development of cherry angiomas.[7]

In this report, we present the case of a 27-year-old married female who experienced a sudden onset of cherry angiomas localized to the breast and neck regions. Clinical evaluation and laboratory investigations revealed severe Vitamin D deficiency, with serum levels significantly below the normal range. In the absence of other systemic or local triggers, we propose that severe Vitamin D deficiency contributed to their development. This case highlights a novel hypothesis linking severe Vitamin D deficiency to cherry angiomas through endothelial and angiogenic dysregulation. Further studies are warranted to explore this association on a larger scale and to elucidate the underlying molecular mechanisms.

2. Case presentation

We describe a 27-year-old Arab female with no significant medical history and genetic or familial predisposition to cherry angiomas. The patient reported the sudden onset of multiple erythematous, dome-shaped lesions, 2 – 5 mm in diameter, predominantly localized to the breast and neck regions (Figure 1). These lesions were asymptomatic but raised concern due to their abrupt appearance and clustering, prompting clinical investigation.

Comprehensive laboratory evaluations were performed to identify potential systemic conditions. A complete blood count revealed normal values: White blood cell count of 6,500/μL (normal: 4,000 – 11,000/μL), hemoglobin level of 13.8 g/dL (normal: 12 – 15 g/dL), and platelet count of 265,000/μL (normal: 150,000 – 450,000/μL). Liver function tests showed aspartate aminotransferase and alanine aminotransferase levels of 25 U/L and 30 U/L, respectively (normal: 10 – 40 U/L and 7 – 56 U/L), excluding hepatic dysfunction. Renal function tests were within normal limits, with a serum creatinine level of 0.9 mg/dL (normal: 0.6 – 1.2 mg/dL) and blood urea nitrogen of 15 mg/dL (normal: 7 – 20 mg/dL), ruling out renal impairment. A lipid profile was within normal ranges, with total cholesterol at 170 mg/dL (normal: <200 mg/dL), triglycerides at 110 mg/dL (normal: <150 mg/dL), high-density lipoprotein at 65 mg/dL (normal: ≥60 mg/dL), and low-density lipoprotein at 90 mg/dL (normal: <100 mg/dL). Thyroid function tests revealed a thyroid-stimulating hormone level of 2.2 mIU/L (normal: 0.4 – 4.0 mIU/L) and free thyroxine at 1.5 ng/dL (normal: 0.8 – 2.8 ng/dL), excluding thyroid dysfunction. Inflammatory markers, including C-reactive protein at 6 mg/L (normal: <10 mg/L) and erythrocyte sedimentation rate at 12 mm/h (normal: 0 – 20 mm/h), were also within normal limits, ruling out systemic inflammation.

However, serum Vitamin D levels revealed a profound deficiency, measuring 3 ng/mL (normal range: 30 – 100 ng/mL). This was the only abnormal finding and warranted further exploration as a potential contributing factor to the pathogenesis of cherry angiomas. Given the absence of other systemic or local triggers, we hypothesize that the patient's severe Vitamin D deficiency may have contributed to endothelial dysfunction and dysregulated angiogenesis. These mechanisms align with emerging evidence linking Vitamin D to vascular stability and capillary proliferation. Vitamin D plays a crucial role in endothelial homeostasis by suppressing pro-angiogenic mediators such as VEGF. A deficiency in Vitamin D may disrupt these pathways, promoting capillary dilation and proliferation, which could explain the sudden onset of cherry angiomas in this patient. This case highlights a novel hypothesis linking severe Vitamin D deficiency to the development of cherry angiomas and underscores the need for further research to investigate the underlying mechanisms.[8]

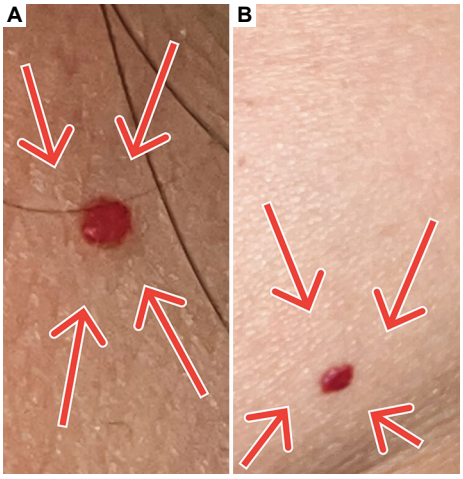

Figure 1. Cherry angiomas present as well-demarcated, erythematous, dome-shaped papules on the skin. (A) A lesion localized to the neck region; (B) A lesion on the left breast. Both lesions are small, measuring approximately 2 – 5 mm in diameter, and exhibit the characteristic red coloration typical of cherry angiomas.

3. Discussion

Cherry angiomas are benign vascular lesions with an unclear pathogenesis. While factors such as aging, hormonal changes, and oxidative stress have been implicated, this case introduces a novel hypothesis linking severe Vitamin D deficiency to the development of cherry angiomas. Vitamin D is essential for vascular health, and its deficiency can lead to endothelial dysfunction and dysregulated angiogenesis, both of which could drive the formation of these vascular lesions.

Vitamin D exerts its biological effects through calcitriol, the active metabolite, which binds to the VDR expressed in endothelial and vascular smooth muscle cells. Through VDR signaling, Vitamin D regulates the expression of angiogenesis-related genes, including those that are involved in the inhibition of pro-angiogenic pathways. A well-documented target of Vitamin D is VEGF, a key driver of capillary proliferation and dilation. Under normal conditions, Vitamin D suppresses VEGF expression, thereby preserving vascular integrity. In states of severe Vitamin D deficiency, VEGF activity may become upregulated, leading to abnormal capillary proliferation and angiogenesis. These mechanisms could explain the sudden onset of cherry angiomas observed in this case. In addition, Vitamin D deficiency is associated with increased oxidative stress and the accumulation of reactive oxygen species (ROS), which exacerbate endothelial damage. ROS disrupts vascular endothelial cell junctions and promotes capillary leakage, potentially contributing to the pathophysiology of cherry angiomas.[9] Moreover, Vitamin D is known to inhibit pro-inflammatory cytokines such as interleukin-6 and tumor necrosis factor-alpha, both of which are implicated in vascular inflammation and remodeling.[10] A deficiency in this anti-inflammatory regulation may further predispose dermal vasculature to aberrant growth and lesion formation.

The dermal microenvironment is also influenced by matrix metalloproteinases (MMPs), enzymes involved in extracellular matrix remodeling and angiogenesis.[11] Studies have shown that Vitamin D deficiency leads to an upregulation of MMP activity, contributing to vascular instability and hyperproliferation.[12] This interplay between MMPs, VEGF, and oxidative stress, in the absence of sufficient Vitamin D, could synergistically drive the formation of cherry angiomas.[13]

In the context of this patient, the severe Vitamin D deficiency (serum level: 3 ng/mL) likely represents a profound disruption in these regulatory mechanisms. The sudden appearance of cherry angiomas localized to the breast and neck regions may reflect heightened vascular vulnerability in these areas, potentially attributed to hormonal or mechanical factors. While the exact molecular triggers remain to be fully elucidated, this case highlights a plausible mechanistic link between Vitamin D deficiency and cherry angiomas, warranting further investigation.

This hypothesis aligns with emerging evidence suggesting that Vitamin D deficiency is not only a marker of systemic health but also a driver of localized vascular pathologies. Given the potential reversibility of vascular abnormalities associated with Vitamin D deficiency, it is plausible that cherry angiomas, particularly those arising in the context of severe deficiency, could regress with adequate Vitamin D supplementation. Emerging evidence suggests that vitamin D repletion can restore endothelial function and modulate pro-angiogenic pathways, including VEGF suppression and oxidative stress reduction. Although no direct studies have investigated the effects of Vitamin D supplementation on cherry angiomas, clinical observations in related vascular conditions provide a rationale for exploring this therapeutic avenue. Future studies should aim to evaluate whether normalizing serum Vitamin D levels through supplementation can mitigate the progression or potentially reverse the development of cherry angiomas in susceptible individuals.

4. Conclusion

This case highlights a novel and plausible link between severe Vitamin D deficiency and the development of cherry angiomas, potentially mediated by mechanisms involving endothelial dysfunction, oxidative stress, and dysregulated angiogenesis. The patient's profound deficiency in

Vitamin D represents a significant disturbance in vascular homeostasis, which may have contributed to the abrupt onset of multiple cherry angiomas. While the exact molecular pathways remain to be fully elucidated, this case underscores the importance of evaluating Vitamin D status in patients presenting with unexplained vascular lesions. Further research is warranted to validate this hypothesis and to investigate therapeutic strategies targeting Vitamin D pathways as a means to prevent or manage such conditions.

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Conflict of interest

The authors declare that there are no conflicts of interest.

Author contributions

Conceptualization: All authors
Investigation: All authors
Methodology: All authors
Writing – original draft: All authors
Writing – review & drafting: All authors

Ethics approval and consent to participate

This case was conducted in accordance with the Declaration of Helsinki and meets the CARE guidelines. Informed consent was obtained from the patient for follow-up, including permission for publication of all photographs, laboratory, and images herein.

Consent for publication

Before taking this case, information was given to the patient, and informed consent was obtained from the patient for follow-up and consent to share the investigations, figures, and any required data.

Availability of data

All data utilized in this manuscript can be made available upon reasonable request. Specifically, anonymized patient data and associated laboratory findings can be provided in compliance with ethical guidelines.

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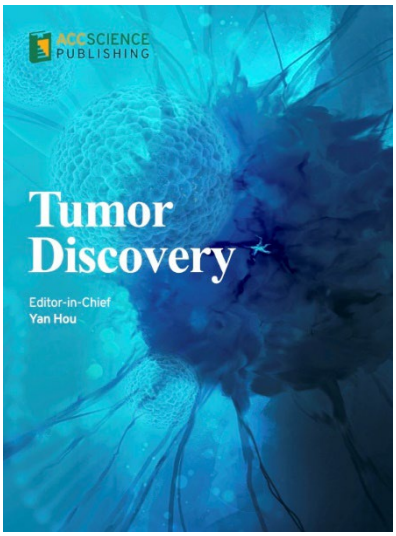

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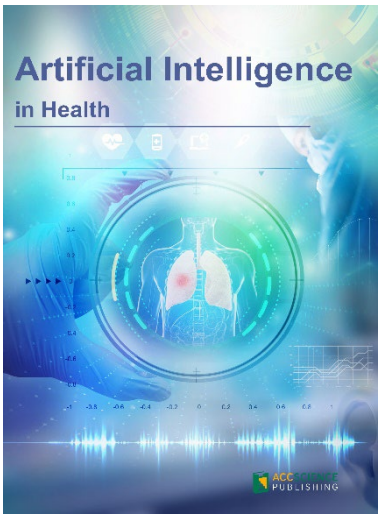

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