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RESEARCH ARTICLE

Predictive modeling of drug efficacy in colorectal cancer via a computational strategy integrating structural descriptors and ranking analysis

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ABSTRACT

Colorectal cancer is challenging to treat because many anticancer drugs do not achieve optimal therapeutic effects. Moreover, these drugs can cause systemic side effects, and patients often respond differently to treatment. This study provides a computational framework that merges quantitative structure-property relationship analysis with a computational methodology combining structural descriptors and ranking analysis to systematically analyze and rank 10 United States Food and Drug Administration approved medicines for colorectal cancer. A suite of degree-based and neighborhood degree-based topological indices were generated and examined for their association with essential physicochemical properties, specially molecular weight and molecular complexity. Correlation research revealed that specific degree-based indices, and neighborhood degree-based indices, exhibited strong predictive power for these properties. By employing ratio weighting alongside with the VIekriterijumsko Kompromisno Rangiranje and Technique for Order Preference by Similarity to Ideal Solution decision techniques, the medicines were ranked based on their predicted physicochemical performance. The results from both decision methods consistently showed fluorouracil as the highest ranked therapeutic agent, followed by tipiracil hydrochloride and bevacizumab, underlining their favorable structural and pharmacological properties. This comprehensive modeling technique provides a consistent and systematic strategy to aid in early-phase drug screening and inform decision-making in colorectal cancer therapy.

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1. Introduction

Colorectal cancer[1] is one of the most commonly observed metastatic tumors and remains the main contributor to cancer-linked deaths. The medicinal treatment of colon-related diseases, primarily relies on chemotherapeutic and immunoregulatory drugs. These treatments frequently involve complex decision-making due to the complex nature of drug effectiveness, toxicity, and patient reaction. Therefore, computational methods have been gradually employed to ease drug screening and ranking, proposing a data-driven methodology for drug development and discovery. Among such methods, graph theory-based topological indices and multi-criteria decision-making (MCDM) methods have gained considerable attention.[2]

Irinotecan is a topoisomerase I inhibitor commonly used in combination regimens for metastatic colorectal cancer. It acts by inducing DNA replication, eventually leading to apoptosis in rapidly dividing tumor cells.[3] Capecitabine is an orally administered fluoropyrimidine carbamate that is enzymatically transformed into 5-fluorouracil (5-FU) in tumor tissues. Its tumor-selective initiation improves tolerability while preserving anticancer efficiency in colorectal cancer patients.[4] 5-FU is a pyrimidine analog that interferes with thymidylate synthase activity, damaging DNA synthesis in cancer cells. It remains a keystone drug in the adjuvant and analgesic cure of colorectal carcinoma[5]

Tucatinib is a selective human epidermal growth factor receptor 2 (HER2) tyrosine kinase inhibitor that has recently been investigated in positive metastatic colorectal cancer. It has demonstrated promising success in overcoming resistance mechanisms associated with previous anti-HER2 therapy.[6] Leucovorin, a reduced folate, is administered in combination with Fluorouracil to stabilize its binding to thymidylate synthase, thereby boosting its cytotoxic effects. Although it lacks standalone anti-tumor activity, it plays a key role in increasing the efficacy of 5-FU.[7] Tipiracil hydrochloride is a thymidine phosphorylase inhibitor co-formulated with trifluridine to increase its bioavailability. It prolongs survival in refractory metastatic colorectal cancer by maintaining effective trifluridine plasma levels.[8] Regorafenib is a multi-kinase inhibitor that targets angiogenesis and oncogenic pathways, offering clinical benefit in treatment-refractory metastatic colorectal cancer. It exerts activity against vascular endothelial growth factor receptor, and rapidly accelerated fibrosarcoma kinases[9]

Bevacizumab is a monoclonal antibody that binds to vascular endothelial growth factor, effectively suppressing angiogenesis associated with colorectal malignant tumors. It is widely used in combination with chemotherapy for metastatic disease management[10] Raltitrexed is a direct inhibitor of thymidylate synthase and serves as an alternative to 5-FU based regimens, especially in patients with cardiac risks. It provides comparable efficacy with potentially improved safety in selected populations.[11] Fruquintinib is a selective VEGFR inhibitor showing efficacy in metastatic colorectal cancer patients who have progressed after standard treatments. It has demonstrated a favorable safety and efficacy profile in late-phase clinical trials.[12]

Graph theory provides a mathematical framework to model molecular structures as graphs, where atoms are represented as vertices and bonds as edges. The transformation of chemical compounds into molecular graphs allows the extraction of topological indices and numerical descriptors that capture structural information.

A graph $\mathbb{G} = (V, E)$ consists of a set V of vertices and a set $E \subseteq \{\{u, v\} \mid u, v \in V, u \neq v\}$ of unordered pairs of distinct elements of V, called edges.[13]

Let $\mathbb{G}$ be a graph and for non-negative integers j and k, let $m_{jk}(\mathbb{G})$ denote the number of edges $uv \in E(\mathbb{G})$ such that the degrees of u and v are j and k respectively, with $j \leq k$. Then, the M-polynomial[14] of $\mathbb{G}$ is defined as Equation (1):

$$M(\mathbb{G}; y, z) = \sum_{j \leq k} m_{jk}(\mathbb{G}) y^j z^k \tag{1}$$

Let $\mathbb{G}$ be a graph and $N(u)$ denote the neighborhood of a vertex $u \in V(\mathbb{G})$. For an edge $uv \in E(\mathbb{G})$, let $d_N(u) = |N(u)|$ and similarly $d_N(v) = |N(v)|$. Then, the neighborhood M-polynomial of $\mathbb{G}$ is defined as Equation (2):

$$NM(\mathbb{G}; y, z) = \sum_{j \leq k} n_{jk}(\mathbb{G}) y^j z^k \tag{2}$$

where $n_{jk}(\mathbb{G})$ denotes the number of edges $uv \in E(\mathbb{G})$ such that $d_N(u) = j$ and $d_N(v) = k$, with $j \leq k$.[15]

To model and forecast molecular properties, reactivity, and biological activity, topological indices[16] derived from the structural representation of chemical compounds have been widely used.

The first Zagreb index is defined Equation (3):

$$M_1(\mathbb{G}) = [\eth_y + \eth_z](M(\mathbb{G}; y, z))|_{y=z=1} \tag{3}$$

The second Zagreb index is defined as Equation

(4):

$$M_2(\mathbb{G}) = [\eth_y \times \eth_z](M(\mathbb{G}; y, z))|_{y=z=1} \quad (4)$$

The harmonic index is defined Equation (5):

$$H(\mathbb{G}) = [2\delta_y J](M(\mathbb{G}; y, z))|_{y=z=1} \quad (5)$$

The forgotten index is defined as Equation (6):

$$F(\mathbb{G}) = [\eth_y^2 + \eth_z^2](M(\mathbb{G}; y, z))|_{y=z=1} \quad (6)$$

The neighborhood first Zagreb index is defined as Equation (7):

$$NM_1(\mathbb{G}) = [S_y + S_z](NM(\mathbb{G}; y, z))|_{y=z=1} \quad (7)$$

The neighborhood second Zagreb index is defined as Equation (8):

$$NM_2(\mathbb{G}) = [S_y \times S_z](NM(\mathbb{G}; y, z))|_{y=z=1} \quad (8)$$

The neighborhood harmonic index is defined as Equation (9):

$$NH(\mathbb{G}) = [2\delta_y J](NM(\mathbb{G}; y, z))|_{y=z=1} \quad (9)$$

The neighborhood forgotten index is defined as Equation (10):

$$NF(\mathbb{G}) = [S_y^2 + S_z^2](NM(\mathbb{G}; y, z))|_{y=z=1} \quad (10)$$

The first neighborhood Gourava index is defined as Equation (11):

$$NGO_1(\mathbb{G}) = [S_y + S_z + S_y S_z](NM(\mathbb{G}; y, z))|_{y=z=1} \quad (11)$$

The second neighborhood Gourava index is defined as Equation (12):

$$NGO_2(\mathbb{G}) = [S_y S_z (S_y + S_z)](NM(\mathbb{G}; y, z))|_{y=z=1} \quad (12)$$

where $\eth_y = \frac{\partial}{\partial y}$, $\eth_z = \frac{\partial}{\partial z}$, $\delta_y = \int_0^y \frac{p(q,y)}{q} dq$, $S_y = \frac{\partial}{\partial y}$, $S_z = \frac{\partial}{\partial z}$, and $J(p(y,z)) = p(y,y)$ are operators.

These indices are instrumental quantitative structure-property relationship (QSPR) models. Recent studies have highlighted the efficiency of various topological indices, such as the Randic index, Zagreb indices, Wiener index, and atom-bond Connectivity index, in predicting biological activity and physicochemical characteristics.[17,18] These indices are mainly suitable for comparing and evaluating the potential of diverse chemical compounds without requiring for experimental assays. For colon medicines, topological modeling offers insights into drug-likeness and molecular interaction potential with target proteins.

Multi-criteria decision Making methods are vital in enhancing drug selection centered on multiple conflicting measures,[19,20] such as efficiency, toxicity, bioavailability, and solubility. Viekriterijumsko Kompromisno Rangiranje (VIKOR) and Technique for Order Preference by Similarity to Ideal Solution (TOPSIS) are two widely used MCDM techniques. The VIKOR technique highlights contradictory criteria for ranking and selecting from a set of alternatives.[21] Based on a measure of closeness to the best solution, it presents a multi-criteria ranking index. The technique maintains a balance between the extreme group efficacy and minimum distinct regret. Lu *et al.* presented a technique that ranks alternatives based on their geometric distance from the ideal and anti-ideal solutions.[22] The alternative closest to the positive ideal solution is considered the best. In the framework of colon drugs assessment, TOPSIS is used to rank drugs by balancing therapeutic effectiveness against minimal side effects. Current research combined MCDM methods with topological indices[23] to rank colon drugs efficiently.[24,25] This increases objectivity and decreases bias by applying decision-making frameworks and structural descriptors.

QSPR modeling and MCDM techniques[26,27] provide a structured framework for modern drug discovery. Topological indices are used in Quantitative structure-property relationship to represent molecular features without laboratory testing, which saves time and cost considerably. VIKOR and TOPSIS[28] complement this by ranking drug candidates across multiple physicochemical criteria, which supports balanced decision-making. Previous studies have shown success in predicting molecular behaviour and identifying promising anticancer agents by combining topological indices with MCDM methods, underscoring the benefits of this integrated strategy for drug screening. This study uses a more inclusive methodology compared to previous works by combining multiple methods, QSPR analysis, and decision-making techniques (VIKOR and TOPSIS). By considering both structural and vital properties such as molar complexity and molar weight, the method offers more reliable and consistent drug rankings, making it a beneficial tool for early-stage drug assessment. This paper is organized in the following manner.

Section 2 comprehensively presents the materials and methods. Section 3 reports and discusses the results, followed by Section 4, which presents the key insights.

2. Materials and methods

In this section Figure 1 illustrates the complete framework of the study. The geometry of the problem is defined by representing each drug molecule as a molecular graph, with atoms as vertices and bonds as edges. Degree and neighborhood degree-based partitions capture essential structural elements such as branching points, and chain segments. These elements are quantified by well established topological indices. These descriptors provide a compact numerical representation of complexity, flexibility, and accessibility factors central to drug pharmacodynamic. Colorectal cancer, which arises from the rectum, a key segment of the large intestine, frequently develops from precancerous lesions. In the early stages, these polyps often remain asymptomatic, making timely detections challenging. As the malignancy progresses, patients may feel some clinical features such as consistent alterations in bowel conditions, abdominal pain, unexplained weight loss, rectal bleeding, and generalized fatigue. This study involves 10 FDA-approved drugs for treating colorectal cancer, as shown in Figure 2.

By applying MCDM method grounded in QSPR analysis, this study highlights the importance of both structural and physical characteristics, particularly molar complexity (Com) and molar weight (MW). The ratio weighting method was employed to assign weights and facilitate the use of the VIKOR method to achieve an optimal ranking of drug elements used for treating colorectal cancer. The chemical descriptors employed in QSPR modeling are comprehensively outlined in Table 1.

The topological indices of the drug 5-FU were computed by using its degree-based partition,
$|E_{2,2}| = 1, \quad |E_{1,3}| = 3, \quad |E_{2,3}| = 4, \quad |E_{3,3}| = 1,$
and neighborhood degree-based partitions.
$|E_{3,5}| = 1, \quad |E_{3,6}| = 2, \quad |E_{5,5}| = 2, \quad |E_{5,6}| = 2, \quad |E_{6,6}| = 2,$
then M-polynomial of 5-FU is calculated as Equation (13):

$$M(\mathbb{G}; y, z) = y^2z^2 + 3yz^3 + 4y^2z^3 + y^3z^3 \quad (13)$$

Using Equations 3 and 13, we get the first Zagreb index (Equation [14]):

$$\begin{aligned} M_1(\mathbb{G}) =&(\eth_y + \eth_z)M(\mathbb{G};,y,z)|_{y=z=1} \\ =&(\eth_y + \eth_z)(y^2z^2 + 3yz^3 + 4y^2z^3 + y^3z^3)|_{y=z=1} \\ =&4 + 12 + 20 + 6 = 42 \end{aligned} \quad (14)$$

Using Equations 4 and 13, we get the second Zagreb index (Equation [15]):

$$\begin{aligned} M_2(\mathbb{G}) =&(\eth_y \times \eth_z)M(\mathbb{G};,y,z)|_{y=z=1} \\ =&(\eth_y \times \eth_z)(y^2z^2 + 3yz^3 + 4y^2z^3 + y^3z^3)|_{y=z=1} \\ =&4 + 9 + 24 + 9 = 46 \end{aligned} \quad (15)$$

Using Equations 5 and 13, we get the forgotten index (Equation [16]):

$$\begin{aligned} F(\mathbb{G}) =&(\eth_y^2 + \eth_z^2)M(\mathbb{G};,y,z)|_{y=z=1} \\ =&(\eth_y^2 + \eth_z^2)(y^2z^2 + 3yz^3 + 4y^2z^3 + y^3z^3)|_{y=z=1} \\ =&34 + 90 + 100 + 122 + 144 = 490 \end{aligned} \quad (16)$$

Using Equations 6 and 13, we get the harmonic index (Equation [17]):

$$\begin{aligned} H(\mathbb{G}) =&(2\delta_y J)M(\mathbb{G};,y,z)|_{y=z=1} \\ =&(2\delta_y)(y^2z^2 + 3yz^3 + 4y^2z^3 + y^3z^3)|_{y=z=1} \\ =&(2\delta_x)(y^4 + 3y^4 + 4y^5 + y^6)|_{y=z=1} \\ =&\frac{2}{4} + \frac{6}{4} + \frac{8}{5} + \frac{2}{6} = 3.93 \end{aligned} \quad (17)$$

Then, neighborhood M-polynomial of 5-FU is calculated as Equation (18):

$$NM(\mathbb{G};,y,z) = y^3z^5 + 2y^3z^6 + 2y^5z^5 + 2y^5z^6 + 2y^6z^6 \quad (18)$$

Using Equations, 7 and 18, we get the neighborhood first Zagreb index (Equation [18]):

$$\begin{aligned} &NM_1(\mathbb{G}) = (S_y + S_z)NM(\mathbb{G};,y,z)|_{y=z=1} \\ =&(S_y + S_z)(y^3z^5 + 2y^3z^6 + \\ &2y^5z^5 + 2y^5z^6 + 2y^6z^6)|_{y=z=1} \\ =&8 + 18 + 20 + 22 + 24 = 92 \end{aligned} \quad (19)$$

Using Equations 8 and 18 we get the neighborhood first Zagreb index (Equation [20]):

$$\begin{aligned} &NM_2(\mathbb{G}) = (S_y \times S_z)NM(\mathbb{G};,y,z)|_{y=z=1} \\ =&(S_y \times S_y)(y^3z^5 + 2y^3z^6 + 2y^5z^5 + \\ &2y^5z^6 + 2y^6z^6)|_{y=z=1} \\ =&15 + 36 + 50 + 60 + 72 = 233 \end{aligned} \quad (20)$$

Using Equations 9 and 18, we get the neighborhood forgotten index (Equation [21]):

$$\begin{aligned} &NF(\mathbb{G}) = (S_y^2 + S_y^2)NM(\mathbb{G};,y,z)|_{y=z=1} \\ =&(S_y^2 + S_z^2)(y^3z^5 + 2y^3z^6 + 2y^5z^5 + \\ &2y^5z^6 + 2y^6z^6)|_{y=z=1} \\ =&34 + 90 + 100 + 122 + 144 = 490 \end{aligned} \quad (21)$$

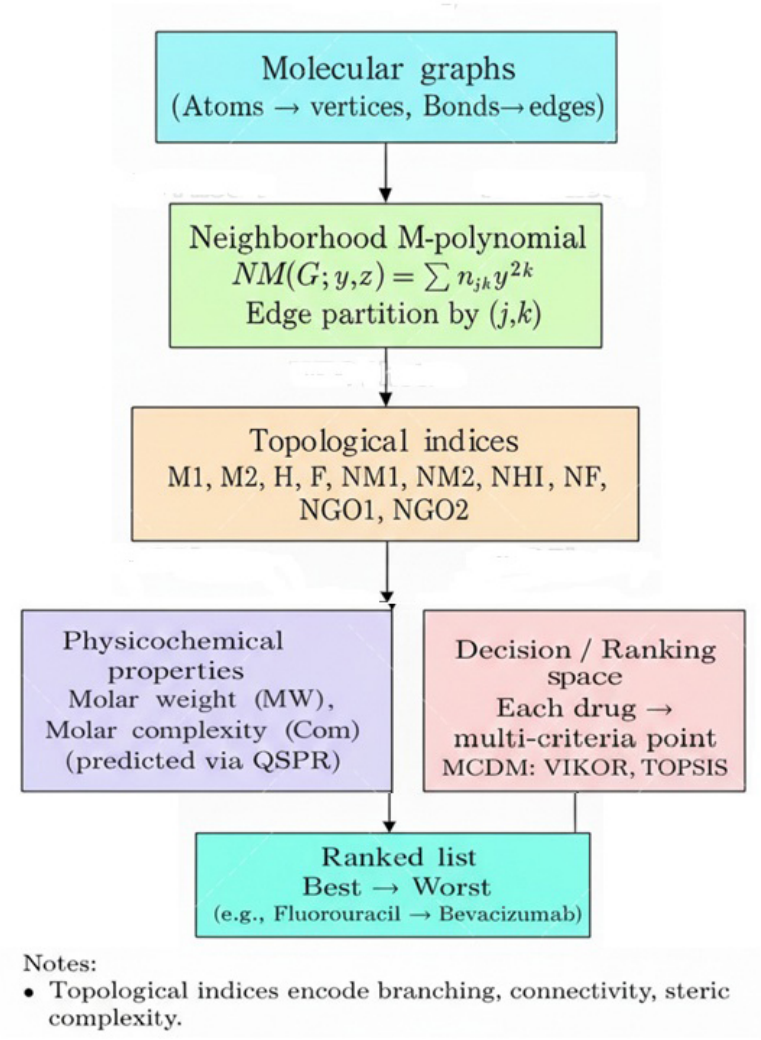

Figure 1. The geometric structure of the problem
Abbreviations: MCDM: Multi-criteria decision-making; QSPR: Quantitative structure-property relationship; TOPSIS: Technique for Order of Preference by Similarity to Ideal Solution; VIKOR: Viekriterijumsko Kompromisno Rangiranje

Using Equations 10 and 18, we get the neighborhood harmonic index (Equation [22]):

$$\begin{aligned} NH(\underline{G}) &= (2\delta_y J)NM(\underline{G};,y,z)|_{y=z=1} \\ &=(2\delta_y)(y^3z^5+2y^3z^6+2y^5z^5+2x^5z^6+ \\ &\quad 2x^6z^6)|_{y=z=1} \\ &=(2\delta_y)y^8+2y^9+2y^{10}+2y^{11}+2y^{12})|_{y=z=1} \\ &=\frac{2}{8}+\frac{4}{9}+\frac{4}{10}+\frac{4}{11}+\frac{4}{12}=1.79 \end{aligned} \tag{22}$$

Using Equations 11 and 18, we get the neighborhood first Gourava index (Equation [23]):

$$\begin{aligned} NGO_1(\underline{G}) &= (S_y+S_z+S_yS_z)NM \\ &\quad (\underline{G};,y,z)|_{y=z=1} \\ &=(S_y+S_z+S_yS_z)(y^3z^5+y^3z^6+ \\ &\quad 2y^5z^5+2y^5z^6+2y^6z^6)|_{y=z=1} \\ &=23+54+70+82+96=325 \end{aligned} \tag{23}$$

Using Equations 12 and 18, we get the neighborhood second Gourava index (Equation [24]):

$$\begin{aligned} NGO_2(\underline{G}) &= [S_yS_z(S_y+S_z)]NM(\underline{G};,y,z)|_{y=z=1} \\ &=[S_yS_z(S_y+S_z)](y^3z^5+2y^3z^6+2y^5z^5+ \\ &\quad 2y^5z^6+2y^6z^6)|_{y=z=1} \\ &=120+648+1,000+1,320+1,728=4,816 \end{aligned} \tag{24}$$

Similarly we can calculate the topological indices of each drug.

Topological indices $M_1(\underline{G})$, $M_2(\underline{G})$, $NM_1(\underline{G})$, $NM_2(\underline{G})$, $H(\underline{G})$, $NH(\underline{G})$, $F(\underline{G})$, $NF(\underline{G})$, $NGO_1(\underline{G})$, and $NGO_2(\underline{G})$ were used in this study to depict the molecular structure of each drug in an appropriate format for computational modeling. These indices have the ability to capture essential features, such as branching and neighborhood relationships within molecular graphs, thereby enabling the structural comparison of

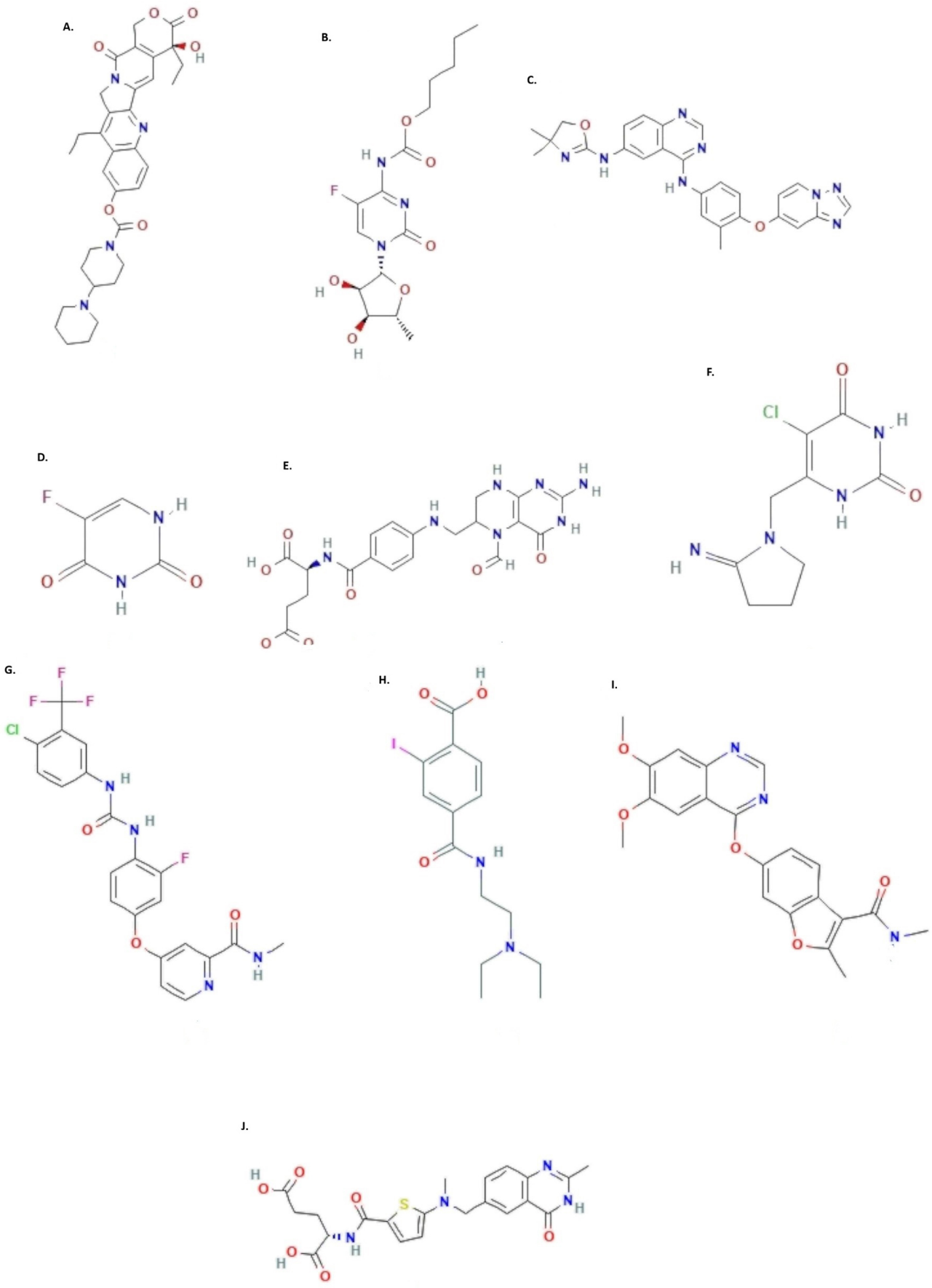

Figure 2. Structures of colorectal cancer drugs. (A) Irinotecan, (B) Capecitabine, (C) Tucatinib, (D) 5-FU, (E) Leucovorin,(F) Tipiracil hydrochloride, (G) Regorafenib, (H) Bevacizumab, (I) Raltitrexed, and (J) Fruquintinib

Table 1. Topological indices of drugs

Drugs	NM_1	NM_2	NGO_1	NGO_2	M_1	M_2	H	F	NH	NF
Irinotecan	617	1992	2609	27358	246	306	20.20	662	8.25	4155
Capecitabine	279	765	1044	9014	124	144	11.27	322	5.16	1617
Fluorouracil	92	233	325	2468	42	46	3.93	108	1.79	490
Tucatinib	792	2441	3233	31324	202	239	16.90	532	10.98	5028
Tipiracil hydrochloride	190	532	722	6272	82	95	7.2	214	3.13	1116
Regorafenib	390	1095	1485	12932	170	195	14.75	454	6.5	2288
Leucovorin	397	1123	1520	13618	172	199	15.47	444	6.89	2351
Bevacizumab	203	521	724	5770	92	103	9.03	232	4.16	1117
Raltitrexed	362	1007	1369	11698	158	181	14.03	408	6.24	2080
Fruquintinib	378	1150	1528	14918	156	189	13.63	406	5.81	2040

medications without the need for laboratory testing. Their strong association with the physicochemical properties of the drugs used for the treatment of colorectal cancer, such as MW and molar Com, makes them effective predictors in QSPR modeling and suitable for integration into decision-making frameworks, including TOPSIS and VIKOR.[29,30]

Table 1, describes 10 different topological indices, comprising degree-based and neighborhood degree-based $(M_1, M_2, NM_1, NM_2H, NH, F, NF, NGO_1, NGO_2)$, for each of the 10 drugs. These indices cooperates as structural descriptors for QSPR modeling.

2.1. Relationship between physicochemical properties and topological descriptors and multi-criteria decision-making techniques

A comprehensive evaluation of the relationship between essential physicochemical properties and topological indices of selected colorectal cancer drugs was conducted. Predictive capabilities of various degree-based and neighborhood-based indices were assessed by applying a QSPR-based modeling framework combined with MCDM techniques.[31,32] The results are organized into subsections highlighting correlation analysis, weight allocation, and final drug rankings obtained through VIKOR and TOPSIS. The association between selected physicochemical properties and topological indices was evaluated using the standard error (SE) and correlation coefficient (r). A low SE value along with an r coefficient close to 1, indicates strong predictive performance. These statistical metrics are essential for assessing the validity of topological indices in modeling physicochemical parameters to drug design.

Table 2 shows the r and SE values between MW and the calculated topological indices. Harmonic index $H(\mathbb{G})$ which had the highest correlation coefficient ($r = 0.9563$), demonstrate high predictive power for physicochemical properties. Table 3 demonstrates correlation coefficient and standard error values between the molar complexity and TI's. $F(\mathbb{G})$ and $M_1(\mathbb{G})$ showed high correlation values $(0.9496, 0.9509)$, that support their role in QSPR modeling for molar complexity prediction.

2.2. Allocation of weights

In this section, we examined the classification of drugs in accordance with their physical and chemical properties, with a focus on QSPR data related to molar Com and MW. The results highlight the effect of solubility on drug performance; compounds with higher solubility exhibited greater therapeutic performance.

To support the ranking process, r were applied as the basis for allocation of weights to the evaluation criterion. Odu[33] introduced the ratio weighting technique, which was applied to compute the weights using the expression $w_j = \frac{r_j}{\sum r_j}$, where r_j. Weights were classified into two categories, beneficial ($w_j > 0.10$) and non-beneficial criteria ($w_j \leq 0.10$), in accordance with the framework proposed by Li et al.[34] The ratio weighting method was chosen because it enables decision makers to prioritize each criteria according to their personal preferences. Weights which are greater than 10% were assumed to have a significant influence in ratio-weighting and MCDM studies.[35,36] The 0.10 threshold for differentiating between beneficial and non-beneficial criterion was reliable with regular procedure.

This cutoff reduced the impact of weakly connected descriptors while maintaining a fair separation of major and minor contributors. Changing this threshold would alter how descriptors are

Table 2. Correlation coefficient for molar weight (MW)

Indices	**SE**	r
$M_1(\underline{G})$	0.1235	0.9370
$M_2(\underline{G})$	0.1366	0.9224
$H(\underline{G})$	0.1033	0.9563
$F(\underline{G})$	0.1290	0.9310
$NH(\underline{G})$	0.1963	0.8313
$NF(\underline{G})$	0.2256	0.7699
$NM_1(\underline{G})$	0.2212	0.7871
$NM_2(\underline{G})$	0.2285	0.7630
$NGO_1(\underline{G})$	0.2267	0.7674
$NGO_2(\underline{G})$	0.2329	0.7524
$NSK_2(\underline{G})$	0.2275	0.7655

Table 3. Correlation coefficient for molar weight (MW)

Indices	**SE**	r
$M_1(\underline{G})$	0.1095	0.9509
$M_2(\underline{G})$	0.1108	0.9496
$H(\underline{G})$	0.1119	0.9486
$F(\underline{G})$	0.1107	0.9497
$NH(\underline{G})$	0.2144	0.7951
$NF(\underline{G})$	0.2148	0.7942
$NM_1(\underline{G})$	0.2194	0.7843
$NM_2(\underline{G})$	0.2195	0.7839
$NGO_1(\underline{G})$	0.2193	0.7844
$NGO_2(\underline{G})$	0.2176	0.7882
$NSK_2(\underline{G})$	0.2186	0.7859

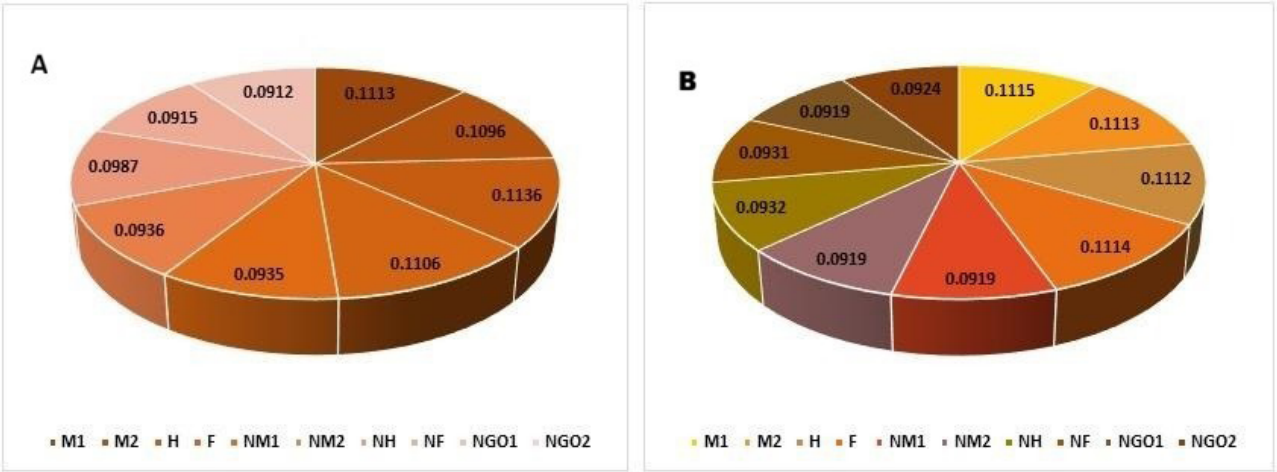

Figure 3. Visualization of allocated weights for (A) molecular weight (B) molecular complexity.

classified: a lower value would allow more indices and increase model complexity, while a larger value would limit the collection of crucial criteria and run the risk of oversimplifying the decision framework.

Figure 3 shows how the weights were split up for both the MW and Com measurements in our quantitative study. It illustrate the weights allocated to each topological index based on their correlation with MW. Indices with weights exceeding 0.10 were considered beneficial, whereas

those with lower weights were deemed as non-beneficial. Figure 3 also shows the index weights used for molar Com, beneficial and non-beneficial categories were determined using the ratio weighting method.

2.3. The Viekriterijumsko Kompromisno Rangiranje

The optimal solution was approximated using the VIKOR technique. Within this framework, each medication under study wsas evaluated using a set of parameters derived from the QSPR modeling used in this analysis. The VIKOR method ranked these options by identifying a solution that represents the closest compromise to the most desired outcome.[37] The foundation for compromise-based decision making in MCDM was first put forth by Bellman & Zeleny[38] and Wan *et al.*[39] in 1973, and by 1998,[40] it had been applied to real-world problems. There are several systematic steps involved in this process. Compared to other established MCDM techniques like TOPSIS, which necessitates an equal number of attributes and alternatives for effective drug ranking, the computational burden tends to be higher.[41]

i Firstly, the ideal best p_i^+ and ideal worst p_i^- values were determined for each criterion $i = 1, \ldots, n$, representing the predicted properties. If the i^{th} function offers a positive effect, then:

$$p_i^+ = \max\{p_{ij}, j = 1, \ldots, m\}, \quad \min\{p_{ij}, j = 1, \ldots, m\} \tag{25}$$

If the i^{th} function is non-beneficial, then:

$$p_i^- = \min\{p_{ij}, j = 1, \ldots, m\}, \quad \max\{p_{ij}, j = 1, \ldots, m\} \tag{26}$$

ii Next, the weighted normalized Manhattan distance O_j and the weighted normalized Chebyshev distance P_j for each alternative $j = \{1, \ldots, m\}$ were computed as follows (Equation [27]):

$$O_j = \sum_{i=1}^{m} w_i \frac{p_i^+ - p_{ij}}{p_i^+ - p_i^-}, \quad P_j = \max_{i=1,\ldots,m} \left(w_i \frac{p_i^+ - p_{ij}}{p_i^+ - p_i^-} \right) \tag{27}$$

where w_i denotes the weight assigned to criterion i.

iii Then, the composite index Q_j for each alternative $j = \{1, \ldots, m\}$ was calculated using Equation (28):

$$Q_j = v \frac{O_j - O^+}{O^- - O^+} + (1 - v) \frac{P_j - P^+}{P^- - P^+} \tag{28}$$

where v reflects the decision-maker's preference toward the group utility, often set as $v = 0.5$, and $(1 - v)$ corresponds to the weight of individual regret.

iv The alternatives were ranked by sorting the values of O_j, P_j, and Q_j in ascending order. Alternatives with lower values were considered more preferable.

Table 4, contains the Manhattan distance (O_j), Chebyshev distance (P_j), and composite index (Q_j) for each drug based on MW. According to the VIKOR-based ranking analysis, 5-FU was identified as the most favorable candidate, followed by tipiracil hydrochloride and bevacizumab, which ranked second and third, respectively. Table 5, based on molar Com, indicated than 5-FU achieved the highest rank, reinforcing its optimal performance.

Figure 4, is derived from the composite Q_i values calculated using the VIKOR method. It incorporates both molar weight and molar complexity-based rankings to assess the overall performance of each drug.

2.4. Drug ranking based on the technique for order of preference by similarity to ideal solution technique

Technique for Order of Preference by Similarity to Ideal Solution is a widely adopted MCDM approach that evaluates and ranks alternatives by measuring their proximity to both an ideal and an anti-ideal solution.[42]

Let $B = \{B_1, B_2, \ldots, B_n\}$ be the set of alternatives and $E = \{E_1, E_2, \ldots, E_m\}$ be the set of assessment criteria. The decision matrix is denoted as $D = [y_{ik}]$, where y_{ik} represents the performance value of alternative B_i with respect to criterion E_k. The weights of the criteria are denoted as w_k, such that $\sum_{k=1}^{m} w_k = 1$. The computational steps for TOPSIS are as follows:

i Step 1: The normalized decision matrix (Equation [29]) was constructed:

$$r_{ik} = \frac{y_{ik}}{\sqrt{\sum_{i=1}^{n} y_{ik}^2}} \quad \text{for } i = 1, 2, \ldots, n;\ k = 1, 2, \ldots, m \tag{29}$$

ii Step 2: The weighted normalized decision matrix (Equation [30]) was constructed:

$$v_{ik} = w_k \cdot r_{ik} \quad \text{for } i = 1, 2, \ldots, n; \quad k = 1, 2, \ldots, m \tag{30}$$

iii Step 3: The positive ideal (PI) and negative ideal (NI) were determined:

Table 4. Viekriterijumsko Kompromisno Rangiranje results of O_j, P_j, Q_j and molar weight-based drug ranking

Drugs	O_j	P_j	Q_j	**MW rank**
Irinotecan	0.8817	0.1136	0.949088	10
Capecitabine	0.33933	0.05126	0.398452	4
Fluorouracil	0	0	0	1
Tucatinib	0.981657	0.0987	0.934419	9
Tipiracil hydrochloride	0.183382	0.022839	0.193928	2
Regorafenib	0.510496	0.075607	0.592795	6
Leucovorin	0.521531	0.080582	0.620312	8
Bevacizumab	0.201548	0.035591	0.259308	3
Raltitrexed	0.460662	0.070529	0.545062	5
Fruquintinib	0.501798	0.081831	0.615759	7

Table 5. Viekriterijumsko Kompromisno Rangiranje results of O_j, P_j, Q_j and molecular complexity-based drug ranking

Drugs	O_j	P_j	Q_j	**Com rank**
Irinotecan	0.327653	0.050716	0.458608	4
Capecitabine	0.3277	0.05026	0.455867	5
Fluorouracil	0	0	0	1
Tucatinib	0.8783	0.0932	1	10
Tipiracil hydrochloride	0.18399	0.022350	0.224646	2
Regorafenib	0.507227	0.074045	0.685992	8
Leucovorin	0.528395	0.078864	0.723896	9
Bevacizumab	0.198158	0.034857	0.299809	3
Raltitrexed	0.458594	0.069018	0.631337	7
Fruquintinib	0.47594	0.066299	0.626625	6

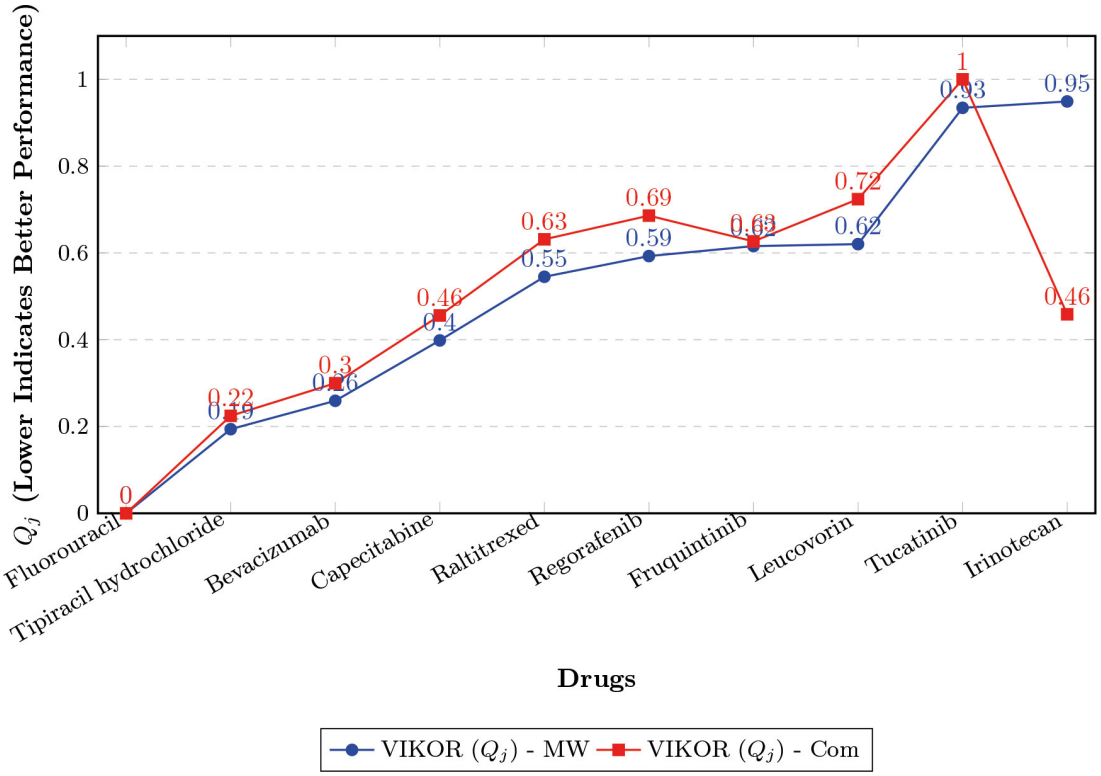

Figure 4. Quantitative structure-property relationship-based ranking of drugs used to treat ranking of drugs used in treatment of colorectal cancer
Abbreviations: Com: Complexity; MW: Molar weight; VIKOR: Viekriterijumsko Kompromisno Rangiranje.

$$B^+ = \{u_1^+, u_2^+, \ldots, v_m^+\}, \quad u_k^+ = \begin{cases} \max(u_{ik}), & \text{if } E_k \text{ is a beneficial scale} \\ \min(u_{ik}), & \text{if } E_k \text{ is a non beneficial scale} \end{cases}$$

$$B^- = \{u_1^-, u_2^-, \ldots, u_m^-\}, \quad u_k^- = \begin{cases} \min(u_{ik}), & \text{if } E_k \text{ is a beneficial scale} \\ \max(u_{ik}), & \text{if } E_k \text{ is a non beneficial scale} \end{cases} \tag{31}$$

iv Step 4: The separation measures (Equation [32]) were computed:

$$S_i^+ = \sqrt{\sum_{k=1}^{m}(u_{ik} - u_k^+)^2}, \quad T_i^- = \sqrt{\sum_{k=1}^{m}(u_{ij} - u_k^-)^2} \tag{32}$$

v Step 5: The relative closeness to the ideal solution (Equation [33]) was calculated:

$$E_i = \frac{T_i^-}{T_i^+ + T_i^-}, \quad \text{for } i = 1, 2, \ldots, n \tag{33}$$

Step 6: The alternatives were ranked in descending order according to the values of E_i. The alternative with the highest E_i was considered the most preferred.

Table 6 shows the ranking of the 10 drugs based on their relative closeness to the ideal solution (E_i) using the TOPSIS method. 5-FU again ranked first, followed by tipiracil hydrochloride and bevacizumab.

Figure 5, presents the comparative rankings of 10 colorectal cancer drugs evaluated using QSPR models integrated with two MCDM techniques, VIKOR and TOPSIS. These models incorporated degree-based and neighborhood-based topological indices, along with physicochemical properties such as MW and Com.

3. Results and discussion

3.1. Comparative analysis of multi-criteria decision-making rankings

Combining QSPR modeling with MCDM methods yielded consistent and strong rankings for the 10 medications used to treat colorectal cancer. Both the VIKOR and TOPSIS approaches found 5-FU to be the best drug for treating cancer. The top three rankings were the same in both methods.

Table 7 presents a comparative evaluation of the selected anticancer drugs using the TOPSIS and VIKOR methods. This means that the medications performed well across the evaluation criteria. The results demonstrate that 5-FU always scored the highest followed by tipiracil hydrochloride and bevacizumab. Figure 6 also depicts these ranking patterns that makes it easy to comprehend how the TOPSIS and VIKOR approaches work. The remarkable agreement between the graphical and numerical studies suggests that the ranking results are robust and reliable.

The topological indices show that 5-FU works better than other drugs because of its best structural properties. 5-FU had the lowest values on most indices ($M_1 = 42$, $M_2 = 46$, $F = 108$, $NM_1 = 92$, etc.). This indicates a balanced molecular complexity, which likely contributes to favorable pharmacokinetic properties, such as improved bioavailability and reduced metabolic liabilities.

3.2. Structural interpretation of top-performing drugs

5-FU, bevacizumab, and tipiracil hydrochloride were the three top ranked drugs due to their structural characteristics. 5-FU shows the simplest molecular structure in the dataset, which means that most of topological indices have low values. This simplicity in structure is linked to a reasonable level of toxicity and well-known clinical effectiveness. Tipiracil hydrochloride shows moderate complexity in indices, which means that there is a balance between drug-like qualities and molecular characteristics that make the drug better performer. Bevacizumab is bigger in molecular size, its neighborhood degree-based indices suggest good atomic conditions.

3.3. Correlation analysis and predictive power

The connection between physical and chemical properties, and topological indices is very important for proving the QSPR. To assess this, the correlation coefficients of 11 topological indices with molecular weight were computed, as illustrated in Figure 7.

Figure 7 shows that most of the indices have positive r with MW, which depicts that these indices are sensitive to molecular structure. The harmonic index $H(\mathbf{G})$ exhibited the strongest correlation coefficient ($r = 0.9563$), followed by first Zagreb index $M_1(\mathbf{G})$ ($r = 0.9370$) and $F(\mathbf{G})$ ($r = 0.9310$). This underscores the efficacy of degree-based indices in representing molecular connection patterns to molar weight prediction.
Figure 8 also demonstrate a comparison of correlation and SEs, which shows how strongly they are associated statistically. The comparatively low values of SE, especially for $H(\mathbf{G})$ and $M_1(\mathbf{G})$, show that the predictions are reliable by using

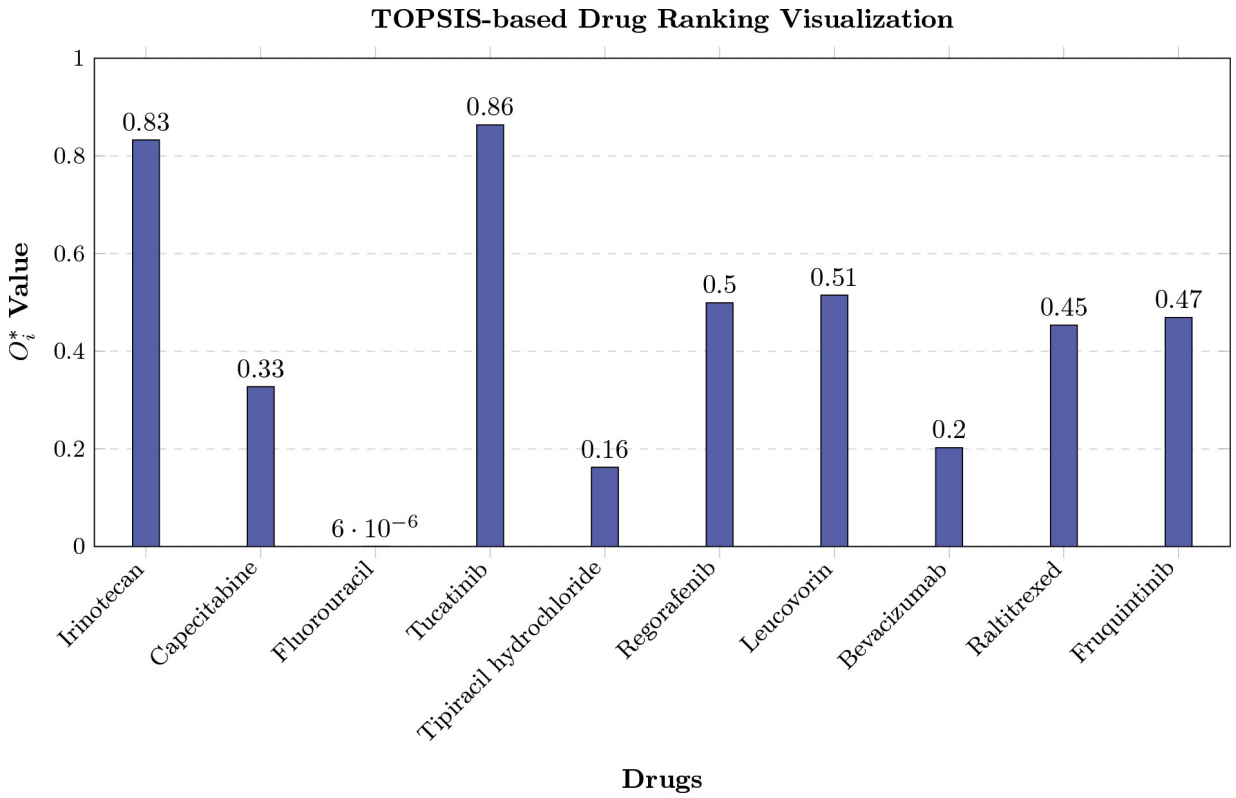

Figure 5. Ranking of drugs using quantitative structure-property relationship models and Technique for Order of Preference by Similarity to Ideal Solution.

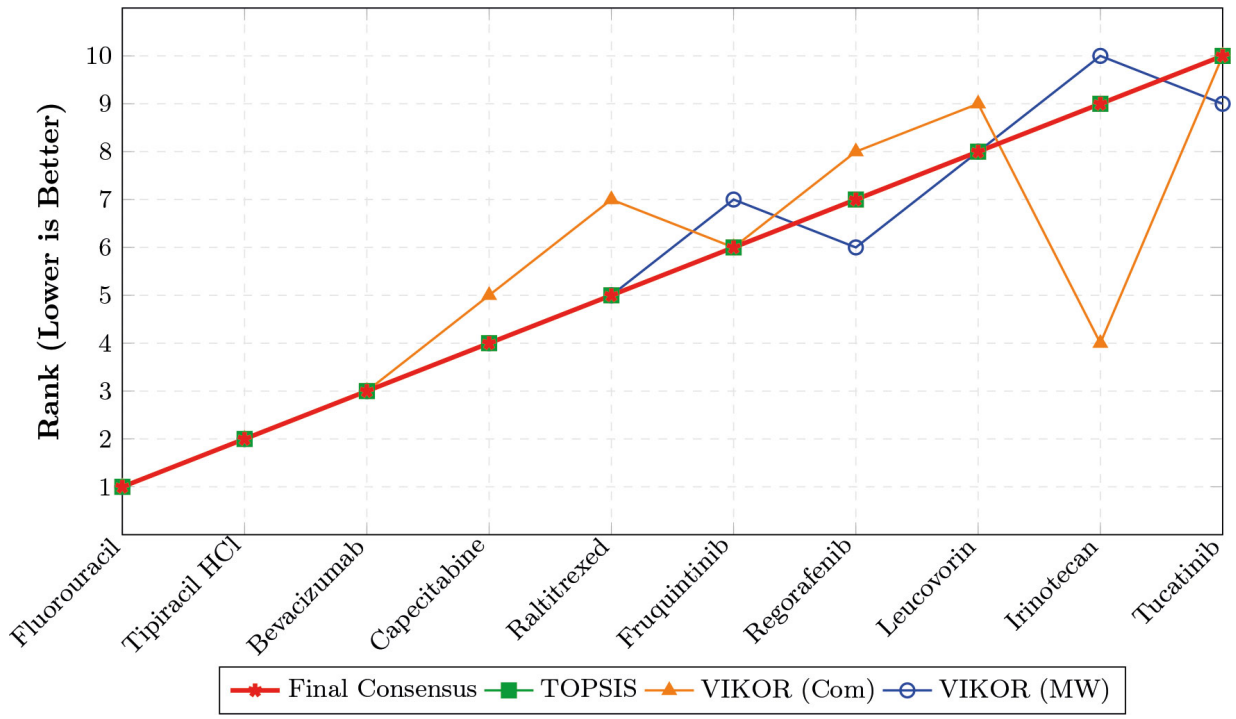

Figure 6. Comparative ranking trends of anticancer drugs using VIKOR and TOPSIS methods. Lower ranks indicate higher performance.
Abbreviations: Com: Complexity; HCl: Hydrochloride; MW: Molar weight; TOPSIS: Technique for Order of Preference by Similarity to Ideal Solution; VIKOR: Viekriterijumsko Kompromisno Rangiranje.

Table 6. Ranking of drugs using Technique for Order of Preference by Similarity to Ideal Solution

Drugs	O_i^*	Rank
Irinotecan	0.832550	9
Capecitabine	0.327282	4
Fluorouracil	0.000006	1
Tucatinib	0.863440	10
Tipiracil hydrochloride	0.162335	2
Regorafenib	0.499051	7
Leucovorin	0.514745	8
Bevacizumab	0.202303	3
Raltitrexed	0.453385	5
Fruquintinib	0.469040	6

Table 7. Comparative ranking of selected anticancer drugs using TOPSIS and VIKOR methods

Drug	VIKOR rank (MW)	VIKOR rank (Com)	TOPSIS rank)	Final consensus)
Fluorouracil	1	1	1	1
Tipiracil hydrochloride	2	2	2	2
Bevacizumab	3	3	3	3
Capecitabine	4	5	4	4
Raltitrexed	5	7	5	5
Fruquintinib	7	6	6	6
Regorafenib	6	8	7	7
Leucovorin	8	9	8	8
Irinotecan	10	4	9	9
Tucatinib	9	10	10	10

Abbreviations: Com: Complexity; MW: Molar weight; TOPSIS: Technique for Order of Preference by Similarity to Ideal Solution; VIKOR: Viekriterijumsko Kompromisno Rangiranje.

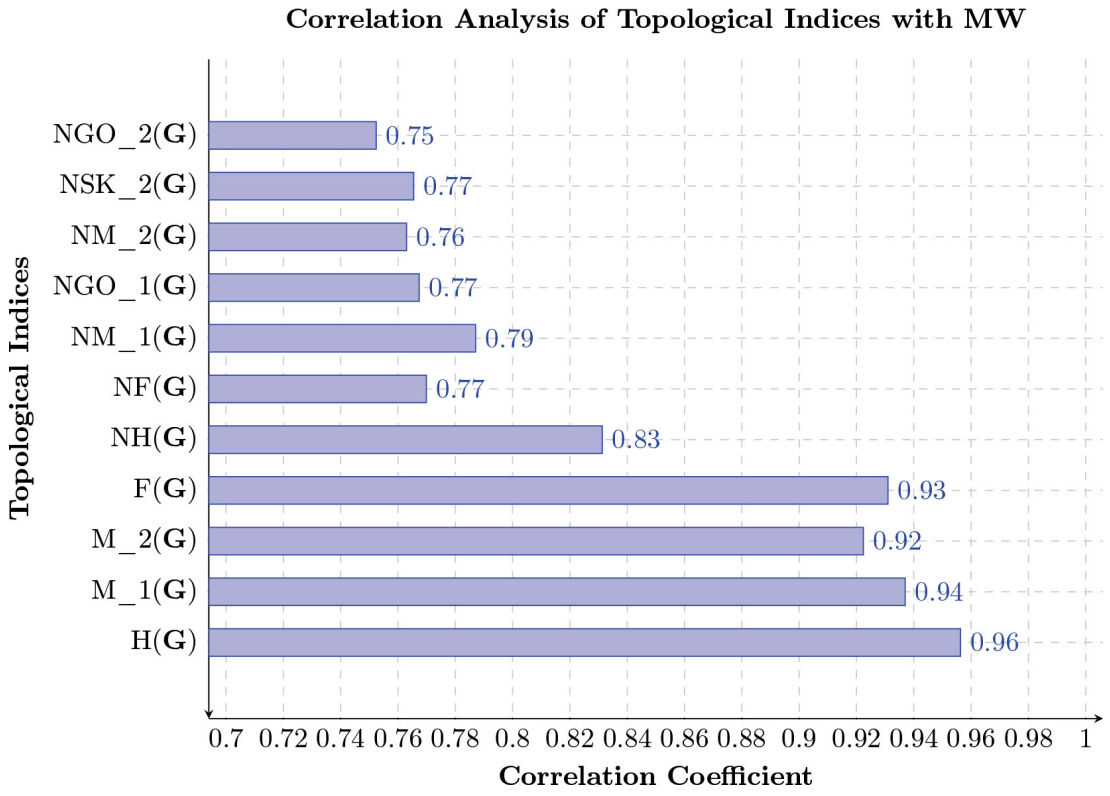

Figure 7. Correlation coefficients of topological indices with molecular weight (MW).

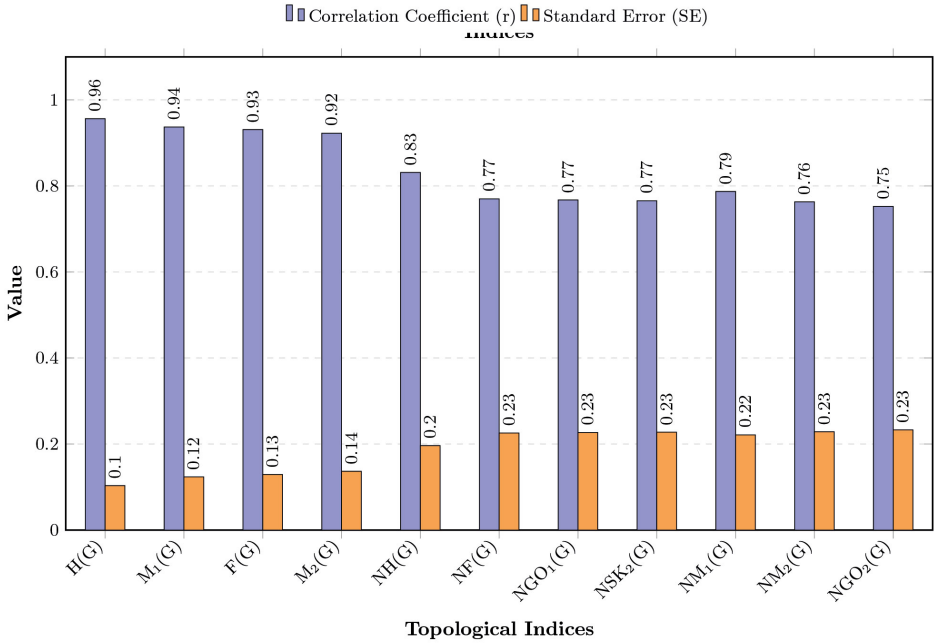

Figure 8. Analysis of standard error and correlation coefficient for topological indices with molar weight.

these indices. This assures that degree-based indices work very well in QSPR modeling as they are sensitive to molecular connectivity.

The results shown in Figures 7 and 8 generally show indicate degree-based indices are better in predictions than neighborhood degree-based indices. These results highlight the efficacy of topological indices in QSPR analysis.

3.4. Statistical analysis of the model

The capability of prediction of our QSPR and MCDM system was assessed by using multiple statistical metrics. The low values of SEs and excellent r show the resilience of our techniques. The results shown in Figure 9 demonstrate that degree-based indices have the highest average correlation for both Com and MW, indicating superior performance overall than neighborhood degree-based indices.

3.5. Consistency analysis between MCDM methods

The agreement between VIKOR and TOPSIS rankings was assessed by using Spearman's rank correlation coefficient.

The high correlation coefficient ($\rho = 0.945$) indicates excellent agreement between the two MCDM methods, validating the consistency and reliability of our ranking approach. Figure 10 illustrates a comparative analysis that shows a significant alignment between the TOPSIS and VIKOR ranking results. This is indicated by a high correlation coefficient of $\rho = 0.945$, which means that both methods of evaluation led to the same decision-making results.

3.6. Limitations of the study

Although this study presents a novel computational paradigm for drug ranking, some limitations should be noted, such as simplifying molecular representation. The analysis of only 10 FDA-approved medications hinders the generalizability of the model. Validation would be enhanced by a larger dataset. The analysis relied solely on topological indices and did not include other crucial molecular descriptors that are critical for absorption, distribution, metabolism, excretion, and toxicity profiling. The computational rankings did not incorporate clinical parameters, limiting clinical applicability without experimental validation.

3.7. Implementation and practical applications

The proposed QSPR-MCDM framework offers several practical implementations in pharmaceutical research and development, such as early-stage drug screening, multi-objective optimization, clinical decision support, drug re-purposing, methodological extension, and open-source tool development. This framework can substantially reduce the cost and time of drug development by providing systematic methods of candidate selection and optimization in colorectal cancer.

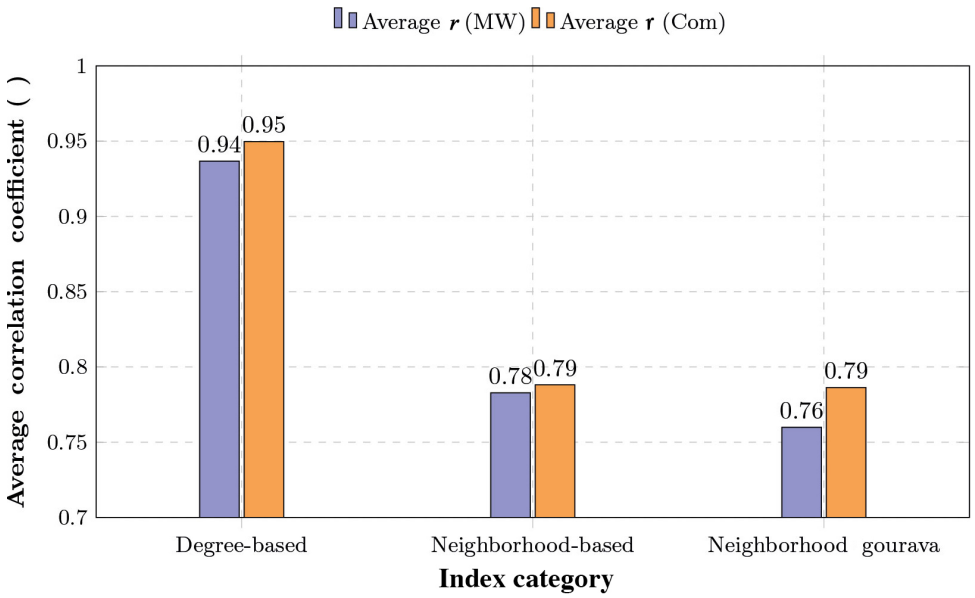

Figure 9. Graphical comparison of average correlation across index categories under molar complexity (Com) and molar weight (MW).

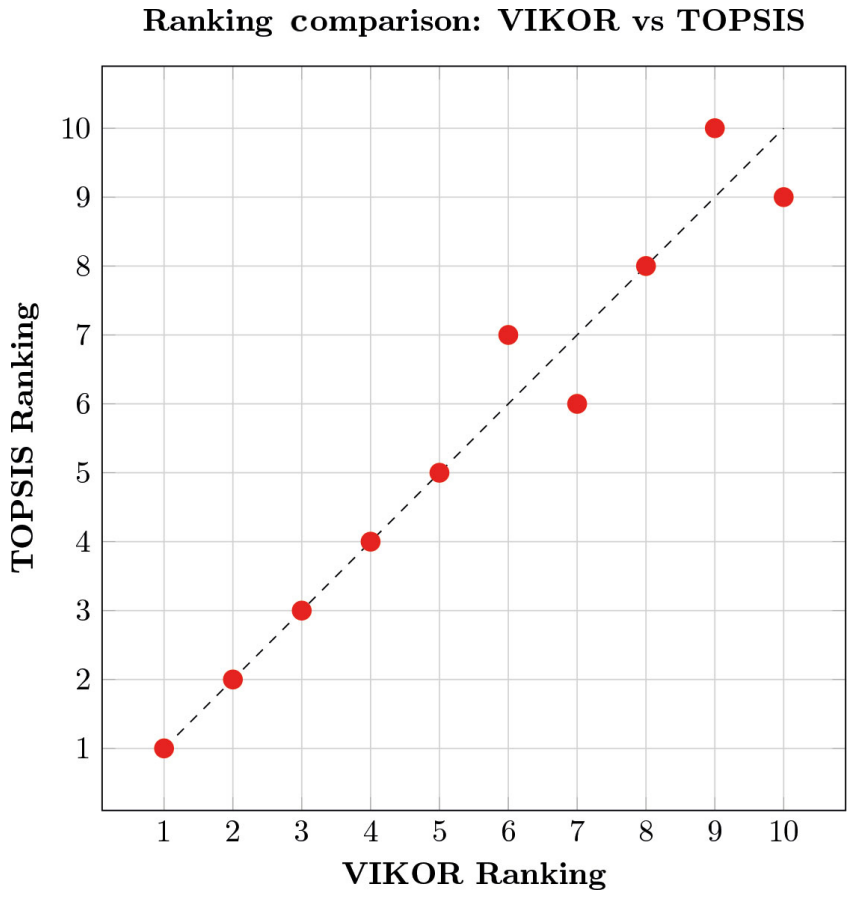

Figure 10. Comparison of rankings between TOPSIS and VIKOR methods showing strong agreement ($\rho = 0.945$)
Abbreviations: TOPSIS: Technique for Order of Preference by Similarity to Ideal Solution; VIKOR: Viekriterijumsko Kompromisno Rangiranje.

4. Conclusion

This study provides an integrated computational framework for QSPR modeling and MCDM techniques to evaluate and rank colorectal cancer treatments. These results imply that the topological indices are effective and can be used to describe important structural characteristics linked to physicochemical properties, especially MW and molecular Com. Correlation analysis showed that the degree-based topological indices, in particular the harmonic index $H(\mathrm{G})$ ($r = 0.9563$), had a better predictive power with MW. This highlights the importance of global molecular connectivity in establishing a drug. 5-FU, as the top-ranked agent in both VIKOR and TOPSIS techniques, followed by tipiracil hydrochloride and bevacizumab, indicates the strength of our approach and supports the structural basis for clinical efficacy. The strong correlation of VIKOR and TOPSIS (Spearman's $\rho = 0.945$) further supports the validity of the ranking results and confirms that the two methods are complementary when applied for drug evaluation. Their usefulness as effective predictors in QSPR modeling of anti-cancer drug evaluation is confirmed by the high r coupled with low SEs. This study contributes to computational drug discovery by offering:

i A methodology for early-phase drug screening.
ii Validation of topological indices as robust structural descriptors for QSPR modeling.
iii A systematic framework for integrating structural information with multi-criteria decision analysis.

The proposed framework has great potential for drug development, particularly in virtual screening of compound libraries and leading optimization stages. Future work should aim to add more molecular indices, use a larger dataset, and validate predictions through experimental studies to increase the predictive potential. The merging of graph theoretical approaches with decision-making methodologies represents a promising direction for computational pharmacology, and, for addressing the complex challenges in cancer drug development. This method not only offers the identification of therapeutic candidates but also provides significant insights into the drug efficacy for colorectal cancer treatment.

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Conflict of interest

The authors declare they have no competing interests.

Author contributions

Conceptualization: Muhammad Akhtar Tarar, Muhammad Kamran, Muhammad Farman
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Availability of data

No data were used to support this study.

AI tools statement

Grammarly was used for the correction of the English grammar.

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