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Prediction of Physicochemical Properties of Flavonoids via Modified Reverse Degree Topological Indices

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Abstract: Flavonoids are naturally occurring compounds with diverse pharmacological properties, including antioxidant, anti-inflammatory, and anticancer activities. They are widely used to treat cardiovascular disorders, neurodegenerative diseases, diabetes, and certain cancers. Understanding their physicochemical properties is important for drug design and development. In this study, we employ modified reverse degree topological indices to predict the physicochemical properties of flavonoid-based drug molecules, such as boiling point, enthalpy of vaporization, flashpoint, polarization, and molar volume. In addition, we develop quantitative structure-property relationship (QSPR) models using linear, quadratic, and cubic regression analyses to estimate the predictive power of these indices. Our results demonstrate that modified reverse degree topological indices achieve high correlation coefficients, outperforming conventional indices in specific cases. This study strengthens their importance in QSPR modeling and their potential applications in drug discovery.

Keywords: modified reverse degree; topological indices; flavonoids; regression model.

1. Introduction

Flavonoids are a diverse group of polyphenolic compounds found abundantly in fruits, vegetables, tea, wine, and medicinal plants. They play a crucial role in plant pigmentation, UV protection, and defense against pathogens. Structurally, flavonoids share a common C6-C3-C6 backbone, consisting of two aromatic rings (A and B) linked by a three-carbon bridge forming a heterocyclic ring (C). Based on structural variations, they are classified into several subgroups, including flavones, flavonols, flavanones, flavanonols, isoflavones, and anthocyanidins [1]. Flavonoids exhibit a wide range of pharmacological activities, primarily due to their strong antioxidant and free radical scavenging properties. Their ability to modulate various biochemical pathways has made them attractive candidates for therapeutic applications.

1.1. Cardiovascular health.

Flavonoids such as quercetin, kaempferol, and catechins have been shown to improve endothelial function, reduce hypertension, and prevent LDL oxidation, thereby lowering the risk of atherosclerosis and coronary artery disease [2].

1.2. Neuroprotection.

Certain flavonoids, including epicatechin and myricetin, have demonstrated neuroprotective effects by reducing oxidative stress, inhibiting neuroinflammation, and promoting synaptic plasticity, which are beneficial in conditions such as Alzheimer's and Parkinson's diseases [3].

1.3. Anti-cancer properties.

Flavonoids interfere with various signaling pathways involved in cancer progression, including apoptosis induction, cell cycle regulation, and angiogenesis inhibition. Genistein, apigenin, and luteolin have been extensively studied for their potential in cancer chemoprevention and therapy [4].

1.4. Diabetes management.

Flavonoids like hesperidin and rutin have been reported to modulate glucose metabolism, enhance insulin sensitivity, and inhibit key enzymes involved in carbohydrate digestion, contributing to their antidiabetic effects [5].

1.5. Anti-inflammatory effects.

By inhibiting cyclooxygenase (COX) and lipoxygenase (LOX) pathways, flavonoids such as baicalein and fisetin exert potent anti-inflammatory effects, making them valuable in the treatment of chronic inflammatory diseases like arthritis and inflammatory bowel disease [6].

1.6. Antiviral and antimicrobial activities.

Many flavonoids exhibit antiviral activity against influenza, herpes simplex virus, and even SARS-CoV-2 by targeting viral replication and host-cell interactions [7]. Additionally, they have demonstrated antibacterial and antifungal effects against pathogenic microbes [8].

Due to these diverse pharmacological properties, flavonoids are extensively studied for their potential in drug discovery and development. Advances in computational modeling and structure-activity relationship studies have further enhanced our understanding of their therapeutic applications.

Quantitative Structure-Property Relationship (QSPR) modeling is an effective approach to predicting the physicochemical properties and biological activities of drug-like molecules based on their molecular descriptors [9]. Topological indices (TIs) play a crucial role in QSPR analysis as they encode structural information of molecules in numerical form, enabling computational predictions of their behavior [10, 11]. There are various topological indices available, which can be classified into four categories: distance, degree, eccentricity, and spectrum-based indices. Chemical structural analyses make considerable use of these indices. The reverse degree inspired a great deal of research into determining and evaluating

topological features for chemical structures and molecular medications in recent years [12-23]. Additionally, as shown by the QSPR models, the modified version of reverse-degree was introduced with higher levels of efficacy [24]. To correlate the molecular structure of flavonoids used to treat tuberculosis with their physicochemical attributes, recent studies have [25-31] developed different QSPR models using various kinds of topological indices.

In our current study, we deal with a relatively large dataset of a diverse range of tuberculosis, heart disease, and cancer drug molecules. The study structure includes calculating modified reverse degree indices for the given dataset (as shown in Figure 1), developing QSPR models related to the physical and chemical characteristics of drug molecules, and conducting comparative analyses of existing regression models.

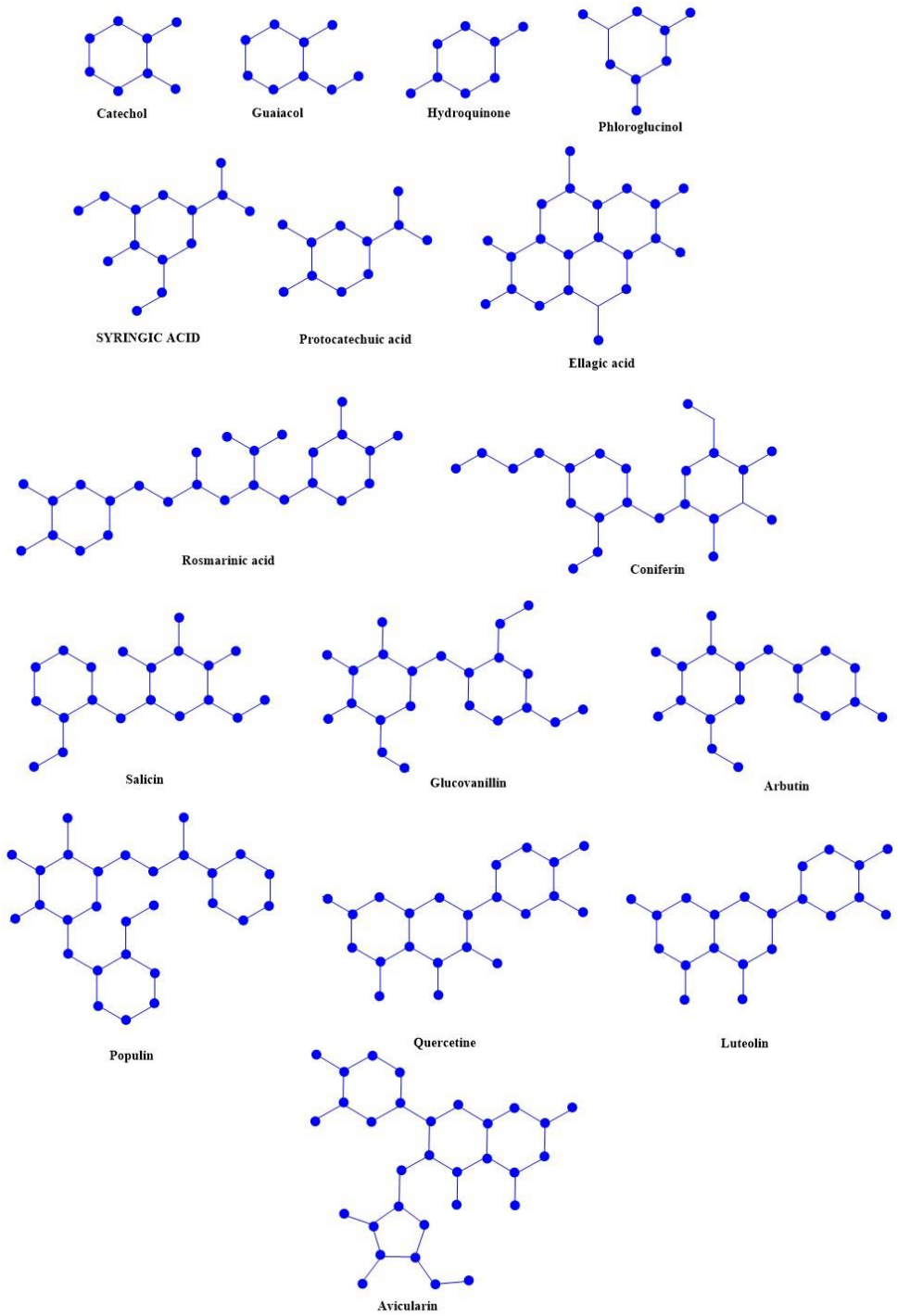

Figure 1. Structure of flavonoids.

2. Modified Reverse Degree-Based Indices

Drug molecules are represented topologically as $2D$ or $3D$ graphs, which are used for analyzing their structural characteristics. The arrangement that results from the drug's chemical composition, excluding hydrogen atoms, is depicted in the graph with the label G for our purposes. The vertex and edge sets of the graph G are represented by the symbols $V(G)$ and $E(G)$, respectively. The $degree$ of a vertex v, denoted by $d(v)$, is defined as the number of edges in G that are incident to v. The maximum degree among all vertices in G is denoted by $\Delta(G)$. In a recent investigation, Arockiaraj et al. [24] proposed an innovative reinterpretation of the reverse degree in the context of molecular graphs. This new approach incorporates a variable metric k, where $k \geq 1$.

The *modified reverse degree* of a vertex v is defined by

$$M_k\Re(d(v)) = \begin{cases} \Delta(G) - d(v) + k & : k \leq d(v) \\ \Delta(G) - d(v) + k(mod\Delta(G)) & : k \geq d(v) \end{cases} \quad (1)$$

Suppose $\Delta(G) = 3$, the modified reverse degrees are computed in the following for $k = 1$, $k = 2$, and $k = 3$, respectively.

$$M_1\Re(d(v)) = \begin{cases} 3, & d(v) = 1 \\ 2, & d(v) = 2 \\ 1, & d(v) = 3 \end{cases}$$

$$M_2\Re(d(v)) = \begin{cases} 1, & d(v) = 1 \\ 3, & d(v) = 2 \\ 2, & d(v) = 3 \end{cases}$$

$$M_3\Re(d(v)) = \begin{cases} 2, & d(v) = 1 \\ 1, & d(v) = 2 \\ 3, & d(v) = 3 \end{cases}$$

The modified reverse degree topological index of a graph G, written $M_k\Re TI(G)$ is characterized by the summation of the modified reverse function $TI(M_k\Re(d(u), M_k\Re(d(v))$, as shown in Table 1. This summation is taken over the edge set of the graph G. By mathematical notation,

$$\begin{aligned} M_k\Re TI(G) &= \sum_{uv \in G} M_k\Re TI(u, v) \\ &= \sum_{uv \in G} TI(M_k\Re(d(u), M_k\Re(d(v)) \end{aligned} \quad (2)$$

By analyzing the pair $(M_k\Re(d(u), M_k\Re(d(v))$, the edges of drug molecules can be categorized into a disjoint union of sets. The two edges $e_1 = u_1v_1$ and $e_2 = u_2v_2$ belong to the same set if they satisfy either of the following conditions:

1. $M_k\Re(d(u_1)) = M_k\Re(d(u_2))$ and $M_k\Re(d(v_1)) = M_k\Re(d(v_2))$, or

2. $M_k\Re(d(u_1)) = M_k\Re(d(v_2))$ and $M_k\Re(d(v_1)) = M_k\Re(d(u_2))$. (3)

Using this classification, the edge set $E(G)$ can be expressed as a disjoint union of subsets:

$$E(G) = \{E_1, E_2, \dots, E_n\},$$

where each edge $uv \in E_i$.

The *modified reverse degree topological index* corresponding to each subset E_i is defined as:

$$M_k\Re TI(E_i) = |E_i| \cdot M_k\Re TI(M_k\Re(d(u), M_k\Re(d(v)),$$

where $|E_i|$ represents the cardinality of the subset E_i. Consequently, the modified reverse degree topological index is derived as follows:

$$M_k\Re TI(G) = \sum_{i=1}^{n} M_k\Re TI(E_i) \qquad (4)$$

This classification and formulation provide a structured approach to analyzing drug molecules based on edge partitions. The detailed methodology and its implications have been explored in [24].

Table 1 gives the expressions for the various modified reverse degree-based topological index functions discussed in the study.

Table 1. Modified reverse degree-based topological index functions.

Topological index function (TI)	Expression
Modified first Zagreb ($M_k\Re M_1$)	$M_k\Re(d(u)) + M_k\Re(d(v))$
Modified atom bond connectivity ($M_k\Re ABC$)	$\sqrt{\frac{M_k\Re(d(u)) + M_k\Re((d(v)) - 2}{M_k\Re(d(u)) \times M_k\Re(d(v))}}$
Modified randić $\left(M_k\Re R_{\frac{1}{2}}\right)$	$[M_k\Re(d(u)) \times M_k\Re(d(v))]^{\frac{1}{2}}$
Modified forgotten ($M_k\Re F$)	$(M_k\Re(d(u))^2 + (M_k\Re(d(v))^2$
Modified geometric-arithmetic ($M_k\Re GA$)	$\frac{2\sqrt{M_k\Re(d(u)) \times M_k\Re(d(v))}}{M_k\Re(d(u)) + M_k\Re(d(v))}$
Modified arithmetic-geometric ($M_k\mathcal{R}AG$)	$\frac{M_k\Re(d(u)) + M_k\Re(d(v))}{2\sqrt{M_k\Re(d(u)) \times M_k\Re(d(v))}}$
Modified first, redefined Zagreb ($M_k\Re ReZ_1$)	$\frac{M_k\Re(d(u)) + M_k\Re(d(v))}{M_k\Re(d(u)) \times M_k\Re(d(v))}$
Modified Second redefined Zagreb ($M_k\Re ReZ_2$)	$\frac{M_k\Re(d(u)) \times M_k\Re(d(v))}{M_k\Re(d(u)) + M_k\Re(d(v))}$
Modified geometric-bi-Zagreb ($M_k\Re GBM$)	$\frac{\sqrt{M_k\Re(d(u)) \times M_k\Re(d(v))}}{(M_k\Re(d(u)) + M_k\Re(d(v))) + (M_k\Re(d(u)) \times M_k\Re(d(v)}$

3. Methodology

We divide the edges according to their degrees to form degree partitions and then add the reverse degrees. Eq.(1) is then used for these divisions to calculate reverse-degree topological indices. To create QSPR models, the calculated indices are then connected with the dataset's physicochemical properties. Table 2 shows the degree partitions of the 16 medicinal compounds that were taken into consideration in our investigation.

Table 2. Degree-based bond partitions of flavonoid-based drug molecules.

Graphs	Drug molecules	The frequencies of degree edge classes				
		(1,2)	(1,3)	(2,2)	(2,3)	(3,3)
G_1	Catechol	0	2	3	2	1
G_2	Guaiacol	1	1	3	3	1
G_3	Hydroquinone	0	2	2	4	0
G_4	Phloroglucinol	0	3	0	6	0
G_5	Syrinic acid	2	3	0	6	3
G_6	Protocatechuic acid	0	4	1	4	2
G_7	Ellagic acid	0	6	0	8	11
G_8	Rosmarinic acid	0	7	3	14	3
G_9	Coniferin	3	3	3	11	5
G_{10}	Salicin	2	3	3	8	5
G_{11}	Glucovanillin	3	3	1	11	5
G_{12}	Arbutin	1	4	2	9	4
G_{13}	Populin	1	4	8	11	6
G_{14}	Quercetin	0	6	1	10	7
G_{15}	Avicularin	0	5	1	12	5
G_{16}	Luteolin	1	7	1	15	10

Numerous mathematical equations are used for every drug and topological index in the mathematical computing process. Hence, we would like to illustrate a specific case for clarity. For the drug molecule Catechol (G_1), the first Zagreb-modified reverse degree indices are calculated as follows:

Firstly, the edge partitions and the reverse degrees of G_1 were obtained for $k = 1, 2, 3$ and tabulated in Tables 3, 4, and 5.

Table 3. Edge partitions and reverse degrees for $k = 1$.

Edge partitions	Reverse degree	Number of repetitions
(3,3)	(1,1)	1
(3,1)	(1,3)	2
(3,2)	(1,2)	2
(2,2)	(2,2)	3

Hence, $M_1\Re M_1(G_1) = 2 \times (3+1) + 1 \times (1+1) + 2 \times (2+1) + 3 \times (2+2) = 28$.

Table 4. Edge partitions and reverse degrees for $k = 2$.

Edge partitions	Reverse degree	Number of repetitions
(3,3)	(2,2)	1
(3,1)	(2,1)	2
(3,2)	(2,3)	2
(2,2)	(3,3)	3

Hence, $M_2\Re M_1(G_1) = 1 \times (2+2) + 2 \times (2+1) + 2 \times (2+3) + 3 \times (3+3) = 38$.

Table 5. Edge partitions and reverse degrees for $k = 3$.

Edge partitions	Reverse degree	Number of repetitions
(3,3)	(3,3)	1
(3,1)	(3,2)	2
(3,2)	(3,1)	2
(2,2)	(1,1)	3

Hence, $M_3\Re M_1(G_1) = 1 \times (3+3) + 2 \times (3+2) + 2 \times (3+1) + 3 \times (1+1) = 30$.

The computing process was applied to the whole dataset in the manner indicated above, and Tables 6, 7, and 8 compiled the results. These values were then compared against various physicochemical properties, including boiling point (BP), enthalpy of vaporization (E), flashpoint (FP), polarization (P), surface tension (ST), and molar volume (MV) of drug molecules. The relevant data were sourced from ChemSpider and PubChem, as detailed in Table 9.

Table 6. The Modified reverse-degree indices $M_1\Re TI(G_i)$ associated with flavonoid-based drug molecules.

Drug structure	$M_1\Re M_1$	$M_1\Re ABC$	$M_1\Re R_{1/2}$	$M_1\Re F$	$M_1\Re GA$	$M_1\Re AG$	$M_1\Re ReZ_1$	$M_1\Re ReZ_2$	$M_1\Re GBM$
Catechol	28	5.169	3.292	56	7.617	8.43	10.7	6.3	2.149
Guaiacol	32	5.766	15.424	64	8.674	9.357	11.7	7.45	2.402
Hydroquinone	28	5.875	13.12	56	7.503	8.552	10.7	6.17	2.126
Phloroglucinol	30	6.692	13.681	60	8.254	9.829	13	6.25	2.44
Syrinic acid	46	8.106	21.58	92	13.214	14.87	20.7	10.15	3.884
Protocatechuic acid	36	6.801	16.585	72	10.235	11.861	16.333	7.7	3.307
Ellagic acid	70	10.558	32.706	122	23.738	26.413	41.999	15.333	7.414
Rosmarinic acid	88	17.736	40.923	170	25.262	28.932	39.333	19.083	7.441
Coniferin	82	14.47	39.1	158	23.908	26.193	36	18.683	6.938

Drug structure	$M_1\Re M_1$	$M_1\Re ABC$	$M_1\Re R_{1/2}$	$M_1\Re F$	$M_1\Re GA$	$M_1\Re AG$	$M_1\Re ReZ_1$	$M_1\Re ReZ_2$	$M_1\Re GBM$
Salicin	68	11.641	32.408	30	20.1	21.99	30.7	15.49	5.867
Glucovanillin	74	13.056	35.1	142	21.908	24.193	34	16.683	6.438
Arbutin	64	11.751	30.105	122	18.93	21.185	29.666	14.2	5.591
Populin	98	17.408	46.934	184	28.814	31.306	42.666	22.533	8.323
Quercetin	72	13	33.534	132	22.624	25.534	38	15.7	6.9
Avicularin	102	17.736	47.787	186	32.184	36.013	53.7	22.45	9.78
Luteolin	70	13.274	32.63	128	21.643	24.501	35.7	15.25	6.547

Table 7. The Modified reverse-degree indices $M_2\Re TI(G_i)$ associated with flavonoid-based drug molecules.

Drug structure	$M_2\Re M_1$	$M_2\Re ABC$	$M_2\Re R_{1/2}$	$M_2\Re F$	$M_2\Re GA$	$M_2\Re AG$	$M_2\Re ReZ_1$	$M_2\Re ReZ_2$	$M_2\Re GBM$
Catechol	38	5.535	18.727	98	7.845	8.162	7.7	9.23	1.861
Guaiacol	44	6.352	21.5	116	8.748	9.277	8.3	10.517	2.049
Hydroquinone	38	5.575	18.626	98	7.804	8.203	7.7	9.133	1.856
Phloroglucinol	39	6.363	18.939	93	8.707	9.305	9.5	9.2	2.184
Syrinic acid	59	10.118	28.403	137	13.439	14.615	15.166	13.7	3.43
Protocatechuic acid	46	7.737	22.454	106	10.7	11.325	12	11	2.722
Ellagic acid	102	17.68	50.811	222	24.495	25.528	26.666	24.6	6.228
Rosmarinic acid	121	18.97	59.192	295	26.317	27.713	27.166	24.97	6.447
Coniferin	121	17.884	55.383	282	24.204	25.872	24.7	26.955	5.89
Salicin	95	14.946	46.302	233	20.399	21.656	20.83	22.7	4.974
Glucovanillin	102	16.551	49.383	246	22.204	23.872	23.333	23.95	5.49
Arbutin	89	14.17	43.434	215	19.455	20.582	20.166	21.216	4.782
Populin	143	20.999	70.333	365	29.415	30.624	27.833	34.616	6.928
Quercetin	102	16.93	49.98	234	23.454	24.57	25	24.5	5.9
Avicularin	146	24.11	71.373	338	33.162	34.888	35	34.916	8.267
Luteolin	101	16.223	49.464	239	22.471	23.55	23.166	24.233	5.536

Table 8. The Modified reverse degree indices $M_3\Re TI(G_i)$ associated with flavonoid-based drug molecules.

Drug structure	$M_3\Re M_1$	$M_3\Re ABC$	$M_3\Re R_{1/2}$	$M_3\Re F$	$M_3\Re GA$	$M_3\Re AG$	$M_3\Re ReZ_1$	$M_3\Re ReZ_2$	$M_3\Re GBM$
Catechol	30	3.713	14.363	70	7.691	8.35	11	6.9	2.14
Guaiacol	32	4.53	15.06	72	8.52	9.545	13	7.117	2.448
Hydroquinone	30	4.68	13.827	70	7.423	8.66	11	6.4	2.101
Phloroglucinol	39	7.02	17.74	99	8.135	9.99	10.5	8.1	2.152
Syrinic acid	63	10.434	29.569	163	13.021	15.111	15.5	13.933	3.318
Protocatechuic acid	50	7.427	23.726	130	10.383	11.701	12	11.3	2.613
Ellagic acid	128	18.107	61.553	356	23.806	26.361	23	29.7	5.515
Rosmarinic acid	115	18.38	53.395	291	24.982	29.31	32.5	24.9	6.622
Coniferin	115	16.557	48.643	260	23.294	26.945	31	22.845	6.238
Salicin	89	13.4	42.033	225	19.753	22.42	25.5	19.933	5.213
Glucovanillin	100	16.557	46.643	256	21.294	24.945	26.999	21.849	5.571
Arbutin	87	13.55	40.8	223	18.656	21.535	23.5	19.216	4.867
Populin	119	16.516	56.264	291	28.388	31.844	39.5	26.716	7.762
Quercetin	114	17.074	54.017	306	22.539	25.67	25	25.7	5.543
Avicularin	160	24.57	75.541	428	31.791	36.525	36	35.816	7.886
Luteolin	105	16.666	49.032	277	21.291	24.959	25.5	23	5.415

Table 9. Physicochemical properties of flavonoid-based drug molecules.

Drug molecule	BP	E	FP	P	ST	MV
Catechol	245	50.2	137	11.9	57.2	86.3
Guaiacol	205	45.9	82.2	13.8	38.7	111.9
Hydroquinone	286	54.6	141.6	11.9	57.2	86.3
Phloroglucinol	331	59.7	174.9	12.6	78.7	84.7
Syrinic Acid	379.5	66.2	155	19.2	51.6	148.4
Protocatechuic Acid	410	69.9	216.3	4.6	84.3	98.8
Ellagic Acid	796.5	119.9	310.1	26.9	140.4	146.2
Rosmarinic Acid	694.7	106.9	254	36.2	84.4	232.8
Coniferin	625.4	97.3	332	34.1	63.1	239
Salicin	549	87.2	285.9	27.1	70.1	190.3
Glucovanillin	574	90.6	216.6	29.9	63.5	212.2
Arbutin	561.6	88.8	293.4	25.3	73.5	174.9

Drug molecule	BP	E	FP	P	ST	MV
Populin	612.2	95.6	217.2	38.9	62.7	275.1
Quercetin	642.4	98.3	248.1	29.1	114.9	168
Avicularin	855.4	130.3	305.8	39.6	129.9	233.2
Luteolin	616.1	94.7	239.5	28.4	92.6	173

4. Statistical Analysis

Techniques combining developments in target-based therapeutic approaches, computational quantum techniques, mathematical methods, molecular docking, and hybrid methodologies are becoming increasingly important in modern drug discovery. Medicinal chemists must employ these strategies to search for new drug discoveries. To try to capture the physicochemical characteristics of novel drug candidates in the pipeline from a cost-effective perspective, we present mathematical predictive models that focus on drugs used for tuberculosis, heart disease, and cancer disorders. Important elements, including the electrical properties, functional groups, and three-dimensional structure, are overlooked, which affects and reduces the accuracy of drug-target interaction predictions. Nevertheless, we believe that the combination of these mathematical techniques with experiments can offer valuable new insights into drug discovery. A quantitative structure-property relationship uses a compound's molecular structure to predict several of its chemical and physical properties. Specifically, the quantitative structure-activity relation model provides a mathematical framework for investigating the complex connection between a molecular compound's structure and its physicochemical or biological characteristics. Topological characteristics play a major role in QSPR analysis, particularly when it comes to predicting and connecting the many physicochemical characteristics of medicines used to treat different illnesses [26-30].

We are now investigating the application of modified reverse degree-based indices in QSPR analysis to evaluate particular physicochemical characteristics of Flavonoids. By comparing Flavonoids' physical and chemical characteristics with the modified reverse degree indices in Tables 10, 11, and 12, we have shown the correlation coefficients.

Table 10. Correlation coefficients between the physicochemical properties of flavonoid-based drug molecules and the indices $M_1\Re TI$.

Physicochemical properties	BP	E	FP	P	ST	MV
$M_1\Re M_1$	0.903662	0.903536	0.745634	0.997841	0.463667	0.952116
$M_1\Re ABC$	0.860020	0.858045	0.697754	0.986297	0.406891	0.948268
$M_1\Re R_{1/2}$	0.893641	0.893576	0.739025	0.997712	0.442948	0.958551
$M_1\Re F$	0.875464	0.874951	0.728645	**0.998273**	0.401326	**0.970843**
$M_1\Re GA$	0.939243	0.939730	0.771245	0.984737	0.553372	0.912984
$M_1\Re AG$	0.947990	0.948300	0.776042	0.982739	0.574909	0.903454
$M_1\Re ReZ_1$	**0.969943**	**0.970825**	**0.792390**	0.955537	0.653755	0.852366
$M_1\Re ReZ_2$	0.883492	0.883444	0.732342	0.996649	0.423427	0.963659
$M_1\Re GBM$	0.957486	0.958058	0.786666	0.972555	0.606204	0.885260

Table 11. Correlation coefficients between the physicochemical properties of flavonoid-based drug molecules and the indices $M_2\Re TI$.

Physicochemical properties	BP	E	FP	P	ST	MV
$M_2\Re M_1$	0.901787	0.901695	0.750078	**0.995059**	0.467717	0.947143
$M_2\Re ABC$	0.944248	0.944595	0.777367	0.984012	0.560521	0.910185
$M_2\Re R_{1/2}$	0.906996	0.907202	0.739615	0.992044	0.488022	0.937850
$M_2\Re F$	0.852985	0.852762	0.696069	0.991092	0.385107	**0.965374**
$M_2\Re GA$	0.944025	0.944478	0.772260	0.983081	0.568188	0.906096
$M_2\Re AG$	0.943118	0.943454	0.775294	0.984990	0.558733	0.911450
$M_2\Re ReZ_1$	**0.967597**	**0.968155**	**0.798087**	0.965793	0.627180	0.871959
$M_2\Re ReZ_2$	0.897292	0.897061	0.740531	0.978930	0.490175	0.925891

$M_2\Re GBM$	0.958429	0.958924	0.786206	0.974256	0.604429	0.886780

Table 12. Correlation coefficients between the physicochemical properties of flavonoid-based drug molecules and the indices $M_3\Re TI$.

Physicochemical properties	BP	E	FP	P	ST	MV
$M_3\Re M_1$	0.977922	0.978596	**0.819997**	0.945590	0.672325	0.837142
$M_3\Re ABC$	0.972802	0.972562	0.805067	0.937964	0.662546	0.829849
$M_3\Re R_{1/2}$	0.979156	0.980376	0.801877	0.933383	0.698202	0.816945
$M_3\Re F$	**0.983979**	**0.985235**	0.804957	0.906984	0.740965	0.775774
$M_3\Re GA$	0.943537	0.944186	0.773201	0.981859	0.568073	0.905706
$M_3\Re AG$	0.943323	0.943463	0.773801	0.985594	0.559461	0.910910
$M_3\Re ReZ_1$	0.836395	0.835961	0.685710	0.990447	0.350031	**0.974917**
$M_3\Re ReZ_2$	0.978769	0.980220	0.801370	0.927642	0.705918	0.809126
$M_3\Re GBM$	0.902168	0.902318	0.739649	**0.994986**	0.471125	0.946593

4.1. Curvilinear regression models.

We explore curvilinear regression analysis to determine the best linear, quadratic, and cubic regression models to predict the physicochemical characteristics of flavonoid-based drug molecules. We employ three regression models to analyze the relationship between the physicochemical property P and the topological index TI:

$$\begin{aligned} &\text{Linear Regression Model: } P = a \times (TI) + d \\ &\text{Quadratic Regression Model: } P = a \times (TI)^2 + b \times (TI) + d \\ &\text{Cubic Regression Model: } P = a \times (TI)^3 + b \times (TI)^2 + c \times (TI) + d \end{aligned} \quad (5)$$

Here, P represents the physicochemical property under consideration, while $a, b, c,$ and d are real-valued constants. The evaluation of these regression models is based on key statistical parameters, including R^2 value, adjusted R^2 value, F-value, and standard error (SE). A comparative analysis of linear, quadratic, and cubic regression models, incorporating the reverse parameter $k = 3$, is provided in Table 10. Furthermore, Figures 2, 3, 4, 5, and 6 show graphical comparisons for these models. In contrast to linear regression equations, the equations in Table 13 indicate that both quadratic and cubic regression models exhibit a significant correlation, offering greater flexibility in modeling. However, in our work, the correlation of quadratic and cubic models is nearly identical. When applied to larger datasets, the consistency of these models may vary, as linear models tend to show higher F-values, suggesting a stronger explanation of variance within the dataset compared to quadratic and cubic models.

Table 13. Statistically optimal regression models determined using the reverse degree parameter $k = 3$.

Property	Model	Equations and statistics
BP	Linear	$P = 1.7526 \cdot M_3\Re F + 138.7397$ SE=35.8, $R^2 = 0.968$, Adjusted $R^2 = 0.966$, $F = 426$
	Quadratic	$P = -0.0008 \cdot (M_3\Re F)^2 + 2.0977 \cdot M_3\Re F + 109.2115$ $R^2 = 0.9705$, Adjusted $R^2 = 0.9660$, S.E = 35.8291, $F = 213.8323$
	Cubic	$P = 0.0000 \cdot (M_3\Re F)^3 - 0.0013 \cdot (M_3\Re F)^2 + 2.2050 \cdot M_3\Re F + 103.3267$ $R^2 = 0.9705$, Adjusted $R^2 = 0.9631$, S.E = 37.2839, $F = 131.6490$
E	Linear	$P = 0.2240 \cdot M_3\Re F + 35.5116$ SE = 4.39, $R^2 = 0.971$, Adjusted $R^2 = 0.969$, $F = 464$
	Quadratic	$P = -0.0000 \cdot (M_3\Re F)^2 + 0.2290 \cdot M_3\Re F + 35.0885$ $R^2 = 0.9708$, Adjusted $R^2 = 0.9662$, S.E = 4.5571, $F = 215.4722$

Property	Model	Equations and statistics
	Cubic	$P = 0.0000 \cdot (M_3\Re F)^3 - 0.0002 \cdot (M_3\Re F)^2 + 0.2702 \cdot M_3\Re F + 32.8237$ $R^2 = 0.9708$, Adjusted $R^2 = 0.9635$, S.E = 4.7336, $F = 133.1526$
FP	Linear	$P = 1.4596 \cdot M_3\Re M_1 + 100.0727$ SE = 42.7, $R^2 = 0.672$, Adjusted $R^2 = 0.649$, $F = 28.7$
	Quadratic	$P = -0.0088 \cdot (M_3\Re M_1)^2 + 2.9544 \cdot M_3\Re M_1 + 50.5658$ $R^2 = 0.7061$, Adjusted $R^2 = 0.6608$, S.E = 41.9674, $F = 15.6133$
	Cubic	$P = 0.0001 \cdot (M_3\Re M_1)^3 - 0.0510 \cdot (M_3\Re M_1)^2 + 6.4894 \cdot M_3\Re M_1 - 28.5644$ $R^2 = 0.7167$, Adjusted $R^2 = 0.6459$, S.E = 42.8811, $F = 10.1206$
P	Linear	$P = 1.0238 \cdot M_3\Re ReZ_1 + 1.8377$ SE = 1.4, $R^2 = 0.981$, Adjusted $R^2 = 0.98$, $F = 722$
	Quadratic	$P = -0.0101 \cdot (M_3\Re ReZ_1)^2 + 1.4933 \cdot M_3\Re ReZ_1 - 2.7543$ $R^2 = 0.9877$, Adjusted $R^2 = 0.9858$, S.E = 1.1654, $F = 523.3801$
	Cubic	$P = -0.0007 \cdot (M_3\Re ReZ_1)^3 + 0.0424 \cdot (M_3\Re ReZ_1)^2 + 0.3017 \cdot M_3\Re ReZ_1 + 5.139$ $R^2 = 0.9889$, Adjusted $R^2 = 0.9861$, S.E = 1.1548, $F = 355.7633$
MV	Linear	$P = 6.3151 \cdot M_3\Re ReZ_1 + 23.6365$ SE = 14.1, $R^2 = 0.95$, Adjusted $R^2 = 0.947$, $F = 269$
	Quadratic	$P = -0.0145 \cdot (M_3\Re ReZ_1)^2 + 6.9880 \cdot M_3\Re ReZ_1 + 17.0558$ $R^2 = 0.9508$, Adjusted $R^2 = 0.9432$, S.E = 14.6237, $F = 125.6550$
	Cubic	$P = 0.0027 \cdot (M_3\Re ReZ_1)^3 - 0.2189 \cdot (M_3\Re ReZ_1)^2 + 11.6252 \cdot M_3\Re ReZ_1 - 13.661$ $R^2 = 0.9513$, Adjusted $R^2 = 0.9391$, S.E = 15.1522, $F = 78.0651$

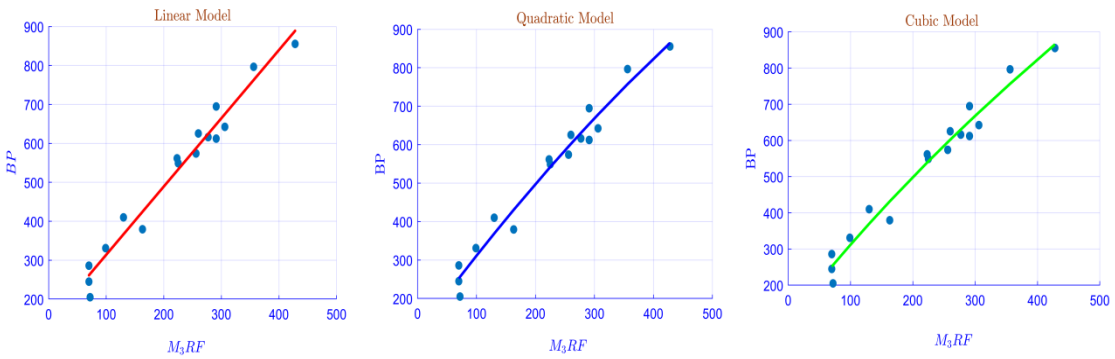

Figure 2. Graphical comparison of linear, quadratic, and cubic regression for boiling point.

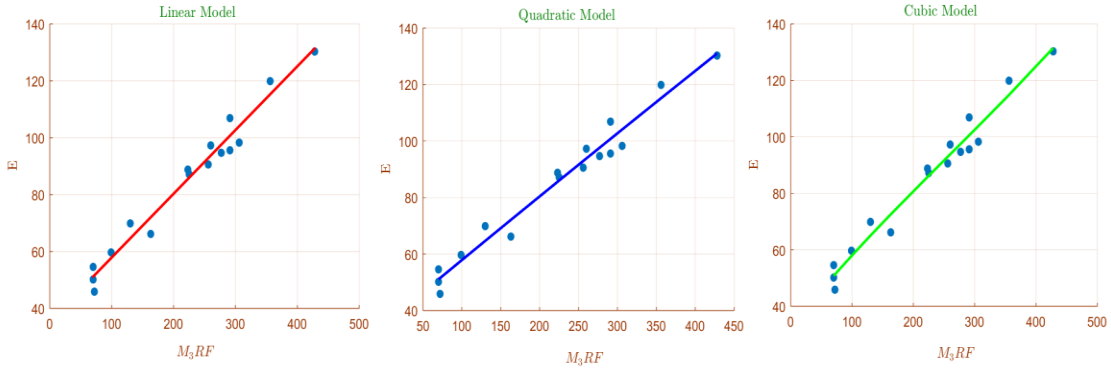

Figure 3. Graphical comparison of linear, quadratic, and cubic regression for enthalpy of vaporization.

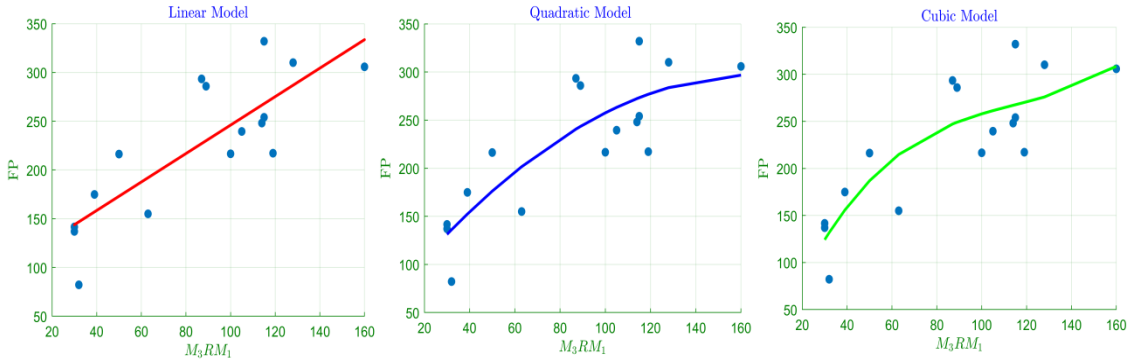

Figure 4. Graphical comparison of linear, quadratic, and cubic regression for flashpoint.

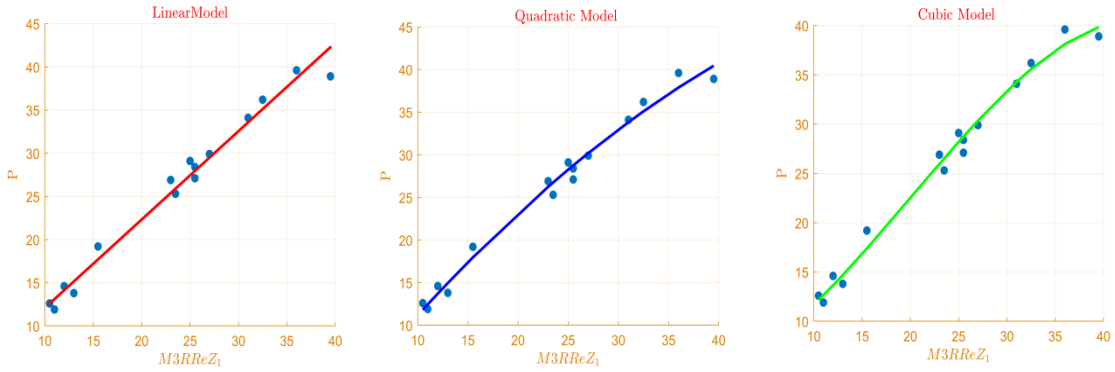

Figure 5. Graphical comparison of linear, quadratic, and cubic regression for polarization.

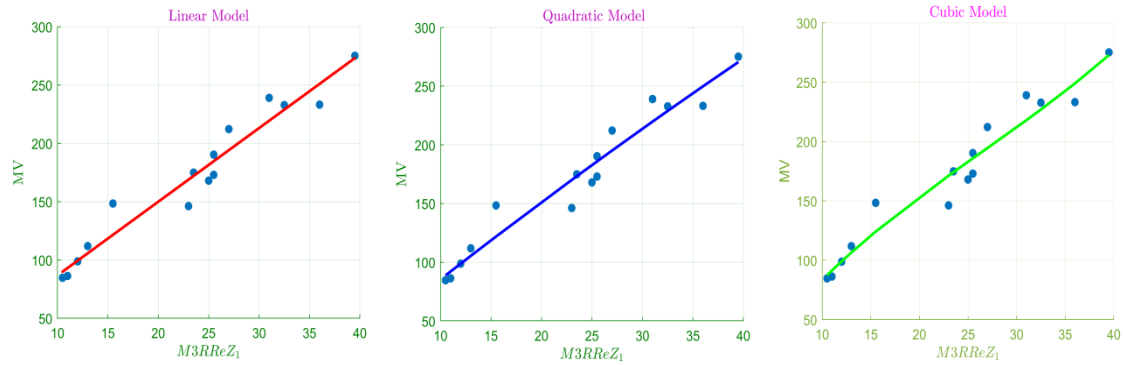

Figure 6. Graphical comparison of linear, quadratic, and cubic regression for molar volume.

4.2. Comparison of actual and computed values for flavonoid-based drug molecules from linear, quadratic, and cubic regression models.

A comparison of the actual and computed values for flavonoid-based drug molecules based on linear, quadratic, and cubic regression models of topological indices is presented in Tables 14-16.

Table 14. Comparison of actual values of boiling point and enthalpy of vaporization vs. predictions by linear, quadratic, and cubic regression models.

Property	**Boiling Point**				**Enthalpy of Vaporization**			
Flavonoids	Linear	Quadratic	Cubic	Actual value	Linear	Quadratic	Cubic	Actual value
Catechol	261	252	251	245	51	51	51	50.2
Guaiacol	265	256	255	205	52	52	51	45.9
Hydroquinone	261	252	251	286	51	51	51	54.6
Phloroglucinol	312	309	309	331	58	58	58	59.7
Syrinic acid	424	430	428	379.5	72	72	72	66.2
Protocatechuic acid	367	368	368	410	65	65	65	69.9

Property	Boiling Point				Enthalpy of Vaporization			
Ellagic acid	763	755	724	796.5	115	117	104	119.9
Rosmarinic acid	649	652	635	694.7	101	102	95	106.9
Coniferin	594	601	589	625.4	94	95	90	97.3
Salicin	533	541	534	549	86	87	83	87.2
Glucovanillin	587	594	583	574	93	94	89	90.6
Arbutin	530	537	530	561.2	85	86	83	88.8
Populin	649	652	635	612.2	101	102	95	95.6
Quercetin	675	676	656	64.4	104	105	97	98.3
Avicularin	889	860	809	855.4	131	133	112	130.3
Luteolin	624	629	614	616.1	98	99	92	94.7

Table 15. Comparison of actual values of flashpoint and polarization vs. predictions by linear, quadratic, and cubic regression models.

Property	Flashpoint				Polarization			
Flavonoids	Linear	Quadratic	Cubic	Actual value	Linear	Quadratic	Cubic	Actual value
Catechol	143.8607	131.2770	122.9176	137	13.0995	12.4499	12.6566	11.9
Guaiacol	146.7799	136.0946	130.1492	82.2	15.1471	14.9517	14.6890	13.8
Hydroquinone	143.8607	131.2770	122.9176	141.6	13.0995	12.4499	12.6566	11.9
Phloroglucinol	156.9971	152.4018	152.8831	174.9	12.5876	11.8118	12.1713	12.6
Syrinic acid	192.0275	201.7650	202.8535	155	17.7066	17.9653	17.3954	19.2
Protocatechuic acid	173.0527	176.2850	180.9056	216.3	14.1233	13.7109	13.6556	14.6
Ellagic acid	286.9015	284.5490	176.2100	310.1	25.3851	26.2487	25.9910	26.9
Rosmarinic acid	267.9267	273.9410	195.3291	254	35.1112	35.1098	35.6998	36.2
Coniferin	267.9267	273.9410	195.3291	332	33.5755	33.8319	34.3846	34.1
Salicin	229.9771	243.8018	215.5181	285.9	27.9446	28.7573	28.7962	27.1
Glucovanillin	246.0327	258.0050	210.3756	216.6	29.4793	30.2010	30.4155	29.9
Arbutin	227.0579	240.9906	215.8447	293.4	25.8970	26.7605	26.5600	25.3
Populin	273.7651	277.5218	189.9791	217.2	42.2778	40.4725	40.0700	38.9
Quercetin	266.4671	273.0018	196.5856	248.1	27.4327	28.2657	28.2442	29.1
Avicularin	333.6087	297.9890	113.7396	305.8	38.6945	37.9149	38.2916	39.6
Luteolin	253.3307	263.7570	206.3101	239.5	27.9446	28.7573	28.7962	28.4

Table 16. Comparison of actual values of molar volume vs. predictions by linear, quadratic, and cubic regression models.

Property	Molar volume			
Flavonoids	Linear	Quadratic	Cubic	Actual value
Catechol	93.1026	92.1693	91.3226	86.3
Guaiacol	105.7328	105.4493	106.4040	111.9
Hydroquinone	93.1026	92.1693	91.3226	86.3
Phloroglucinol	89.9450	88.8312	87.3951	84.7
Syrinic acid	121.5206	121.8862	123.9929	148.4
Protocatechuic acid	99.4177	98.8238	98.9850	98.8
Ellagic acid	168.8838	170.1093	170.7710	146.2
Rosmarinic acid	228.8773	228.8502	225.6304	232.8
Coniferin	219.4046	219.7493	216.7926	239
Salicin	184.6715	185.8212	185.2112	190.3
Glucovanillin	194.1379	195.1551	193.7793	212.2
Arbutin	172.0413	173.2662	173.6835	174.9
Populin	273.0829	270.4582	270.3959	275.1
Quercetin	181.5140	182.6933	182.3436	168
Avicularin	250.9801	249.8318	247.1226	233.2
Luteolin	184.6715	185.8212	185.2112	173

When evaluating the predictive performance presented in Tables 14, 15, and 16, an interesting trend emerges. While linear models exhibit higher F-values, indicating stronger explanatory power, cubic models introduce greater complexity. Quadratic models often strike a balance between goodness-of-fit and simplicity. Although quadratic and cubic models

generally achieve slightly higher R^2 and adjusted R^2 values compared to linear models, the improvements are not always substantial. Additionally, quadratic models tend to have lower standard errors (SE), suggesting better overall precision in capturing data variability without unnecessary complexity. This indicates that, among linear and cubic models, quadratic models provide a more reliable and practical choice for predicting the examined properties of flavonoids, as further supported by Figures 7 and 8. It emphasizes that evaluating a model's performance should not be based on just one metric. Instead, multiple factors should be considered, such as the model's ability to generalize well and make accurate predictions on new, unseen data. This is especially important in fields like machine learning and statistics, where overfitting training data can lead to poor real-world performance.

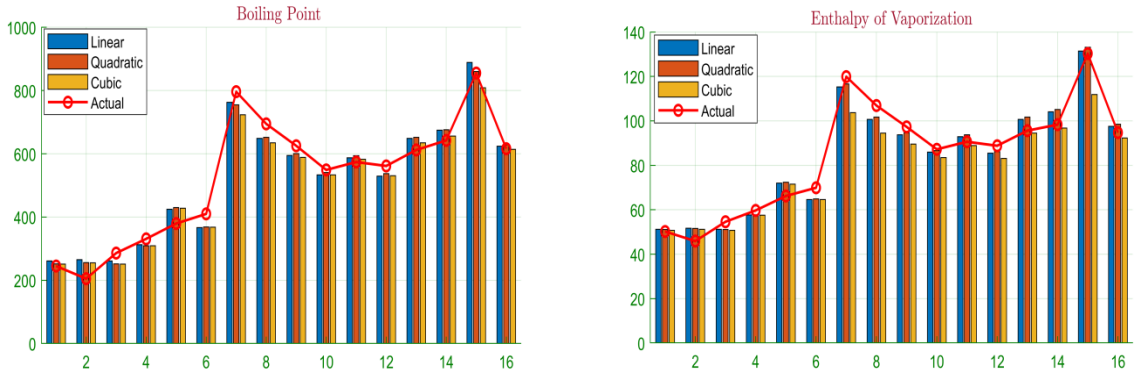

Figure 7. Comparison of actual and predicted values for boiling point and enthalpy of vaporization.

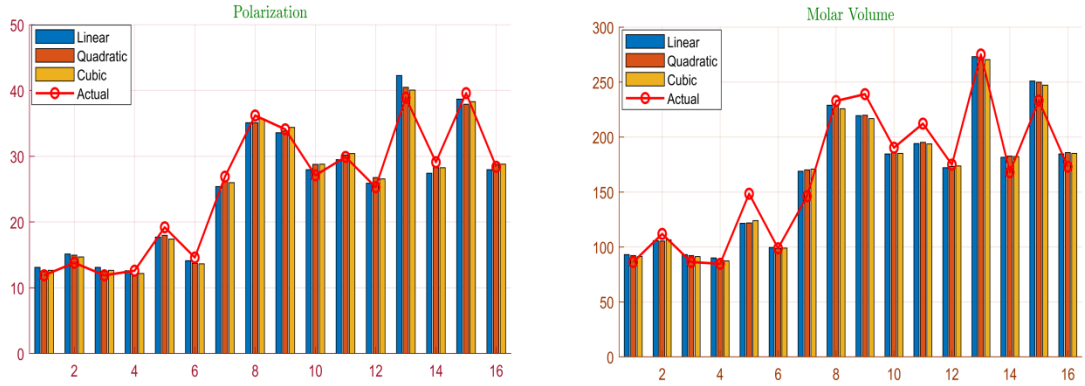

Figure 8. Comparison of actual and predicted values for polarization and molar volume.

5. Comparative Analysis

We now compare the predictive accuracy of the five proposed models with those identified in the literature on flavonoid-based drug molecules [25]. The following observation regarding the boiling point was made in [25]. Eq.(6) was developed by proposing a dataset of thirteen medicinal compounds that showed the strongest correlation for the Y-index ($Y(G)$).

$$BP = 437.65577 - 2.5726 \cdot Y(G) + 0.01044024(Y(G))^2, \mathrm{R} = 0.9666 \qquad (6)$$

However, the model we suggested in the current work contains the modified reverse arithmetic and uses a dataset of sixteen flavonoid-based drug molecules. According to Eq.(7), the modified forgotten index has the highest correlation.

$$BP = -0.0008 \cdot (M_3\Re F)^2 + 2.0977 \cdot M_3\Re F + 109.2115, \mathrm{R} = 0.9851 \qquad (7)$$

The comparison of correlation coefficients for various physicochemical parameters demonstrates the strong predictive capability of our model. Our model yields higher correlation values for enthalpy of vaporization ($R = 0.9852$ vs. 0.9664) and polarization ($R = 0.9938$ vs. 0.9801), indicating an improved relationship between predicted and actual values. Although the correlation for flashpoint ($R = 0.8465$) is slightly lower than that reported in [25] ($R = 0.8636$), and the correlation for molar volume ($R = 0.9750$) is marginally lower than [25] ($R = 0.9818$), the overall trend suggests that our approach provides a more accurate representation of key physicochemical properties.

6. Conclusion

In this study, we provided topological characterizations of flavonoid-based drug molecules used for treating various diseases by utilizing variable degree metrics instead of traditional fixed degrees through reverse degree edge partitions. Through QSPR analysis, we developed robust predictive models by comparing linear, quadratic, and cubic regressions to estimate the physicochemical properties of flavonoid pharmaceutical drugs. Notably, our comprehensive analysis highlighted the superiority of quadratic models in predicting specific properties over linear and cubic models. Our findings suggest that different modified topological indices are well-suited for predicting specific physicochemical properties of flavonoid-based drug molecules. The modified Forgotten index is suitable for the boiling point and enthalpy of vaporization, while the modified First Zagreb index is effective for the flashpoint. The modified Geometric-Bi-Zagreb index is appropriate for polarization, and the modified first Redefined Zagreb index is ideal for molar volume. Notably, no topological index successfully predicts surface tension.

Author Contributions

Conceptualization, K.K., U.V.C.K., and H.M.N.; computational analysis, K.K., U.V.C.K., and H.M.N.; writing—original draft preparation, H.M.N. and N.N.; writing—review and editing, H.M.N. and N.N. All authors have read and agreed to the published version of the manuscript.

Institutional Review Board Statement

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Informed Consent Statement

Not applicable

Data Availability Statement

Data supporting the findings of this study are available upon reasonable request from the corresponding author.

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Conflicts of Interest

The authors declare no conflict of interest.

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