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Topological Study of Hydroxychloroquine Conjugated Molecular Structure Used for Novel Coronavirus (COVID-19) Treatment

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ABSTRACT

The novel coronavirus disease 2019 (Covid-19) is a mutating and recombining pandemic that potentially spreading through an infected person in droplet-generated forms that have affected more than 200 countries and endanger the entire globe. There is no clear strategy for the care of COVID-19 cases. Moreover, experts across the globe are working actively to develop medicinal or anti-virus drugs. On the basis of recent clinical findings and recommendations, the study examined a variety of new medications that have shown antiviral activity against SARS-CoV-2, among other drugs, antimalarial medications Chloroquine (CQ) and Hydroxychloroquine (HCQ) have gained significant publicity to have promising effects against SARS-CoV-2. Linking a bioactive substance to a biocompatible polymer typically provides various concerns, such as improved drug solubilization, improved modification, precise restriction, and controlled discharge. An enormous number of medical analyses have confirmed that the characteristics of medical drugs have a nearby connection with their atomic structure. Medication properties can be acquired by considering the atomic structure of relating drugs. The calculation of the topological index of a medication structure empowers researchers to have a superior comprehension of the physical science and bio-organic attributes of drugs. Ev-degree and ve-degree based topological indices are two novel degrees based indices as of late defined in graph theory. Ev-degree and ve-degree based topological indices have been defined as corresponding to their relating partners. In this paper, we have computed topological indices based on ev-degree and ve-degree for the Hydroxyethyl Starch and Hydroxychloroquine (HCQ-HEC) bioconjugate molecular structure.

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1. Introduction

Over hundreds of years, viruses and contagious diseases have become the focus of research and medicine. Virology has involved some of our greatest scientific challenges and triumphs, from smallpox to HIV and so many others. Today is no different, Virology is once again at the front-line of the latest epidemic of the novel coronavirus, SARS-CoV-2, and its related infectious disease COVID-19. Following the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) in 2003[1,2] and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in 2012,[3–5] COVID-19 is the third novel coronavirus to cause a large-scale epidemic in the 21st century. The first case of the novel coronavirus (2019-nCoV) was identified on 31 December 2019 in the city

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of Wuhan China, the capital of Hubei province. The troubling aspects of COVID-19 are its obvious potential to transmit quickly and its tendency to induce serious condition in older adults and patients with chronic health conditions. The Covid-19 is a mutating and recombining pandemic that potentially spreading through an infected person in droplet-generated forms that have affected more than 200 countries and endanger the entire globe. The control of SARS-CoV-2 appears to be the highest priority from the medical care and global viewpoint, including clinical acuity stimulation strategies available to prevent Covid-19 and the handling of critically ill patients as well as large-scale research must proceed rapidly.[6–9]

The COVID-19 pandemic presents a major danger to public health systems around the world. The rising number of cases/patients and deaths globally led the world community about the worst possible scenarios. The collaborative approach of the medical and scientific world to the Covid-19 epidemic is based on gathering the latest data possible through diagnosis, care, and management process. The World Health Organization (WHO) partnering with the Global Research Collaborative on Infectious Disease Preparedness (GLOPID-R) developed the Covid-19 Study Roadmap in January 2020 (www.glopid-r.org). Despite knowledge about the infectious cycle of SARS-CoV-2, there is no clear strategy for the treatment of COVID-19 patients. Meanwhile, scientists across the world are aggressively working to discover therapeutic treatments or anti-virus vaccinations. On the basis of recent scientific results and guidelines, research reviewed numerous new drugs that have demonstrated antiviral action against SARS-CoV-2. Among many drugs, antimalarial drugs Chloroquine (CQ) and Hydroxychloroquine (HCQ) have earned much attention to provide positive results against SARS-CoV-2. HCQ is a CQ derivative that has the same mode of action but a better formulation, making it a perfect medication for the treatment of malaria, viruses and autoimmune diseases.[10–13] Several alternative molecular pathways of HCQ activity against SARS-CoV-2 have been suggested with approval of the FDA. On 28 March 2020, the FDA approved the emergency use of hydroxychloroquine (HCQ) for COVID-19.[14] Antimalarial medications may cause ventricles, QT prolongation, and other heart damage that may pose a specific danger to patients with chronic diseases.[15] In this article, we are attempting to study the topological properties of hydroxychloroquine polymeric conjugated molecular structure.

A significant proportion of new drugs/medicine are manufactured annually from the chemical labs and put them into the market after some research trials. Initially, the large numbers of test and researchs are needed to detect their toxicity, side effects and biological activity on the human body. To test these drugs requires high laboratories and budget which is very costly for low budget countries. Scientists compared a significant quantity of chemical compounds experiment with their molecular structure and concluded the drug properties.[16,17] The properties of medicines or drugs are strongly linked to their molecular structure according to a lot of scientific studies. Pharmaceutical properties of drugs can be obtained by observing the molecular structure of the related drug using the method of chemical graph theory. Mathematical chemistry connect graph theory to science and focuses its consideration on the ideas of chemical graphs known as a molecular graph where molecules atoms are represented by vertices and bonds by edges. In fact, topological theories have often been used in the field of chemistry, the topology of an atom determines the form of prominent Huckel sub-atomic orbitals. Normally the vertex degree is referred to its valence in a chemical graph.

Chemical graph theory takes an important role in the view and preparation of any synthetic structure or organization of substances. Topological indices are numerical quantities that describe the topological properties of the chemical structures. These indexes are referred to as graph invariant. Such indexes can be used individually or in combination with other numerical descriptors to extract a quantitative structure-property or structure-activity relationship (QSPR/QSAR). In the QSPR/QSAR analyses, scientists are interested in studying the topology of the chemical network using certain mathematical constant/parameters obtained from the molecular structures

of networks.[18,19] Chemicals Graph Theory have numerous applications linked to medicine, drug design, medical research and in experimental science.[20,21]

In theoretical chemistry, topological indexes are numerical functions correlated with the chemical structures for the association of chemical types form with various physical properties, reactivities of chemical or biological behaviors. These topological indexes are obtained from the structures of molecules. Numerous fascinating models have been effectively extracted when different molecular indexes have been used. Topological indices are playing an important role. In the most part, topological indices identified by the definition of vertex degrees. Topological indexes have been used to explain and improve the statistical features of drugs. The topological descriptor concept firstly given by Wiener[22] when he was working on the breaking point of paraffin. He found first topological index name as the Wiener index. The most widely used topological indices in chemical and mathematical literature are the Randic, Zareb and Wiener indices.[23–25]

Zhong[26] described an index name as Harmonic index and thereafter Ediz et al.,[25] described noval new Harmonic index. All of the above research was performed by using the classical definition of degrees. Chellali et al.[27] recently presented two novel definitions in the field of graph theory, namely ve-degree and ev-degree. Later Horoldagva et al.[28] explored some of ve-degree and ev-degree based mathematical concepts. The classical degree-based frameworks then have been transformed into ve-degree and ev-degree Zagreb and Randic indices in.[29–31] The ve-degree Zagreb index has been shown to have a greater predictive ability than the classic Zagreb index.

In this paper we have explored the ve-degree and ev-degree-based topological characteristics of Hydroxyethyl starch conjugated with Hydroxychloroquine (HCQ-HEC). We have evaluated the Zagreb (M^{ev}) and the Randic (R^{ev}) indexes based on *ev*-degree, first Zagreb α-index ($M_1^{\alpha ve}$), first Zagreb β-index ($M_1^{\beta ve}$), Randic index (R^{ve}), second Zagreb index (M_2^{ve}), atom-bond connectivity (ABC^{ve}) index, harmonic (H^{ve}) index, geometric-arithmetic (GA^{ve}) index and sum-connectivity (χ^{ve}) index based on *ve*-degrees to predict some physicochemical properties for molecular structure of Hydroxyethyl starch conjugated with Hydroxychloroquine (HCQ-HEC). The functions of topological indices in pharmaceutical research has been improved. Topological indices catch molecular structure stability and offer a statistical framework for predicting properties such as viscosity, boiling points, gyration distance, etc. In all situations where the IUPAC suggestions are relevant for terminology used in molecular biology and computational drug discovery. For more about these topological indices and formulas see.[32–39]

2. Preliminaries

Throughout this section, we present few initial ideologies. A connected graph denoted by $G = (V, E)$ with edges set E and of vertices set V. The degree of the v vertex, denoted by Λ, is the amount of specific edges that may be incident to the v vertex. The open neighborhood of the v vertex, denoted by $N(v)$, is a collection of all vertices adjacent to the v vertex. closed neighborhood of v, denoted by $N[v]$, describes as the union of v vertex with open neighborhood $N(v)$ of v vertex. The ev-degree, denoted by $\Lambda_{ev}(e)$, of any edge $e = uv \in E$ is the total vertices quantity of the closed neighborhoods union of u and v vertex. The ve-degree, denoted by $\Lambda_{ve}(v)$, of any vertex $v \in V$ is the number of different edges that appears to any vertex in the closed neighborhood of v.

The Bioconjugate in chemistry is the study of linking one molecule to another by means of chemical and biological strategy.

The ev-degree and ve-degree based topological descriptor are defined below (see Table 1). In this paper, we will compute the below given topological descriptor for molecular structure of Hydroxyethyl starch conjugated with Hydroxychloroquine (HCQ-HEC).

Table 1. Ev and Ve degree based topological indices.

The Zagreb index based on *ev*-degree	The first Zagreb α-index based on *ve*-degree
$M^{ev}(G)=\sum_{e\in E}\Lambda_{ev}(e)^2$	$M_1^{\alpha ve}(G)=\sum_{v\in V}\Lambda_{ve}(v)^2$
The Randic index based on *ve*-degree	**The atom-bond connectivity index based on *ve*-degree**
$R^{ve}(G)=\sum_{uv\in E}(\Lambda_{ve}(u)\times\Lambda_{ve}(v))^{-\frac{1}{2}}$	$ABC^{ve}(G)=\sum_{uv\in E}\sqrt{\frac{\Lambda_{ve}(u)+\Lambda_{ve}(v)-2}{\Lambda_{ve}(u)\times\Lambda_{ve}(v)}}$
The first Zagreb β-index based on *ve*-degree	**The second Zagreb index based on *ve*-degree**
$M_1^{\beta ve}(G)=\sum_{uv\in E}(\Lambda_{ve}(u)+\Lambda_{ve}(v))$	$M_2^{ve}(G)=\sum_{uv\in E}(\Lambda_{ve}(u)\times\Lambda_{ve}(v))$
The Randic index based on *ev*-degree	**The geometric-arithmetic index based on *ve*-degree**
$R^{ev}(G)=\sum_{e\in E}\Lambda_{ev}(e)^{-\frac{1}{2}}$	$GA^{ve}(G)=\sum_{uv\in E}\frac{2\sqrt{\Lambda_{ve}(u)\times\Lambda_{ve}(v)}}{\Lambda_{ve}(u)+\Lambda_{ve}(v)}$
The harmonic index based on *ve*-degree	**The sum-connectivity index based on *ve*-degree**
$H^{ve}(G)=\sum_{uv\in E}\frac{2}{\Lambda_{ve}(u)+\Lambda_{ve}(v)}$	$\chi^{ve}(G)=\sum_{uv\in E}(\Lambda_{ve}(u)+\Lambda_{ve}(v))^{-\frac{1}{2}}$

3. Methodology and main results

In this paper we discussed the $M^{ev}, M_1^{\alpha ve}, M_1^{\beta ve}, M_2^{ve}, R^{ve}, R^{ev}, ABC^{ve}, GA^{ve}, H^{ve}$ and χ^{ve}. We also covered the closed formulas for molecular structure of Hydroxyethyl starch conjugated with Hydroxychloroquine (HCQ-HEC) to compute all given indices.

For calculation, we have utilized the combinatorial processing strategy, edge partition technique, vertex partition strategy, analytic procedures, graph hypothetical tools, techniques of counting degrees and entirety techniques of degree neighbors. Moreover, Matlab programming have been utilized for the numerical computations and checks. We likewise utilized the maple for plotting these numerical outcomes.

4. Hydroxychloroquine

The COVID-19 pandemic proceeds to grasp the world in both transparent and hidden ways from almost unseen yet mysterious adversaries swapping capacities. Currently, there is no FDA-approved COVID-19 medication but high-level initiatives and investigations are underway. However, on 28 March 2020, the FDA permitting for the emergency use of chloroquine (CQ) and hydroxychloroquine (HCQ) in COVID-19.[14]

Hydroxychloroquine is chloroquine derivatives, was developed in 1955 and approved for malaria treatment. Hydroxychloroquine is included in the list of the World Health Organization's important drugs with a better safety profile, especially with sustained usage. Hydroxychloroquine has expanded over the years to include autoimmune diseases such as rheumatoid arthritis, Sjogren syndrome, systemic lupus erythematosus, and post-Lyme disease arthritis.[40,41]

4.1. Motivation

As a particular group of biomolecules, smart polymers manifest an amazing reaction to physico-chemical and biological shift when their circumstances have a minor intervention, such as shifts in PH interest, ion disruption, magnetization, light and temperature. These polymers are therefore also defined as environmentally sustainable systems or responsive stimulation. As good drug delivery mechanisms, such frameworks have broad applications in the medical field, for example, smart nucleic acid polymers or intracellular protein distribution, much like nucleus or ribosome in tissue regeneration. A special type of smart polymer or polymeric hydroxychloroquine (HCQ) conjugated with hydroxyethyl starch (HES) is commonly utilized in the production of anticancer medicines. The development of QSARs utilizing basic molecular techniques seems to be a powerful and

complementary tool for drug-protein, high-throughput screening, docking and computational chemistry. All QSAR techniques are focused on the use of molecular/topological descriptors that are mathematical tools to codify useful chemical knowledge and allow for similarities between antioxidant and statistical processes. The uses of molecular/topological descriptors in medicinal chemistry has been a rational approach to huge synthesis and screening of compounds. QSAR models estimate biological behavior by using different types of structural molecular parameters as inputs. Among such parameters, topological indices (TIs) are a very fascinating class.

4.2. Structure

In this section, we review the molecular structure of hydroxychloroquine (HCQ) used in the treatment of malaria which is recently suggested for emergency used in COVID-19 and computed the novel degrees based topological descriptors such as $M^{ev}, M_1^{\alpha ve}, M_1^{\beta ve}, M_2^{ve}, R^{ve}, R^{ev}, ABC^{ve}$, GA^{ve}, H^{ve} and χ^{ve}, respectively.

HES is produced by chemical alteration of ethylene oxide from human products, such as waxy maize starch. Hydroxyethylation improves the solubility and decreases the enzymatic oxidation of starch by serum amylases, thereby increasing the half-life of the plasma. This improvement in biostability depends on the average substitution per anhydroglucose unit (AGU) and the substitution ratio between C_2 and C_6.[42,43] The optimization of these combinations resulted in a sufficiently extended half-life of plasma that enabled HES to be converted into the medical setting as a polymeric blood volume splitter.[44]

HES formulated with hydroxychloroquine (HCQ) as a new polymeric product capable of inhibiting the aggressive existence of pancreatic cancer cells (PCs). HES was conjugated with HCQ using a simple pairing of carbonyldiimidazole to prepare chloroquine-modified HES (CQ-HES) (see Figure 1). HCQ-HES has the ability to create novel antimetastatic therapies as a drug delivery mechanism ideal for future production of chemotherapeutics. Throughout tumor distribution applications, these nanoparticle systems benefit from special tumor biology by enhanced permeability and retention (EPR) effects and allow for increased tumor aggregation.[45–47]

Let $\mathcal{G}$=HCQ-HES graph that containing $53n+2$ vertices and $56n+2$ edges (see Figure 2). The vertices with degree 1, 2, and 3 denoted by V_1, V_2, and V_3, respectively. Where $|V_1| = 9n+2, |V_2| = 27n$, and $|V_3| = 17n$. On the bases of degrees the vertices partition of HA-Dox is given in Table 2. Similarly on the bases of degrees HCQ-HES having edges partition given in Table 3.

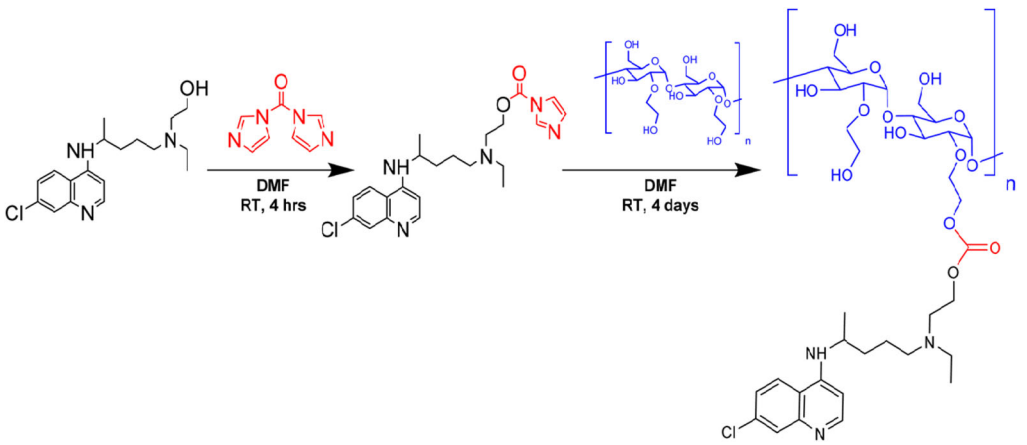
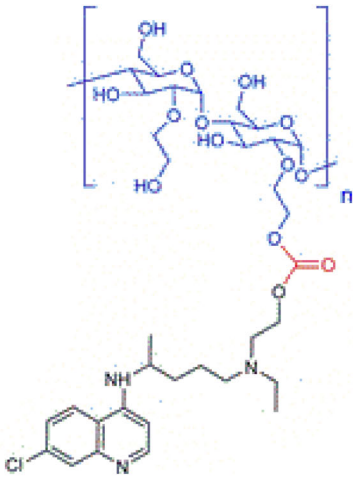
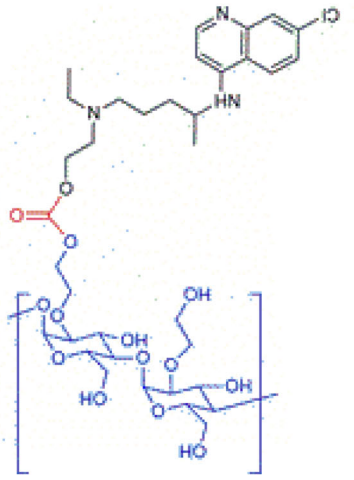


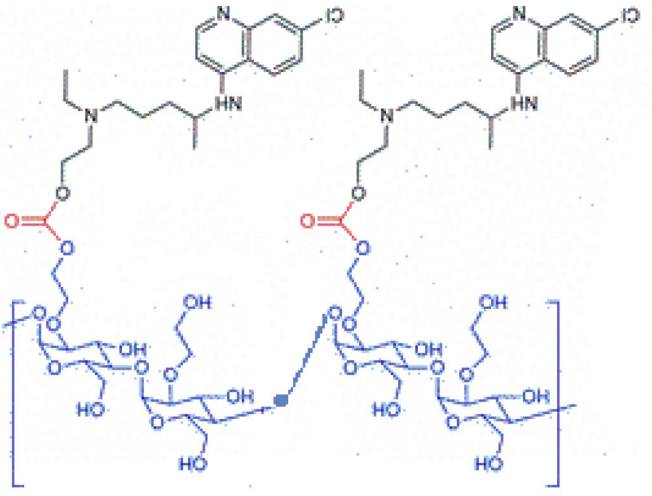
Figure 1. HES conjugated with HCQ.



(a) Chemical Structure



(b) Unit Chemical Structure



(c)

Figure 2. Molecular structures of HCQ-HES.

Table 2. Vertex partition for different value of *m*.

[***n***]	[1]	[2]	[3]	[4]	[5]	[6]	[7]	[8]	[9]	[10]
V_1	11	20	29	38	47	56	65	74	83	92
V_2	27	54	81	108	135	162	189	216	243	270
V_3	17	34	51	68	85	102	119	136	153	170
Total vertex	55	108	161	214	267	320	373	426	479	532

Table 3. Ev-degrees partition.

$(\boldsymbol{deg}(u), \boldsymbol{deg}(v))$	ev-degree	Frequency
(2, 1)	3	$4n+1$
(3, 1)	4	$5n+1$
(2, 2)	4	$112n$
(3, 2)	5	$25n$
(3, 3)	6	$10n$

- **The Zagreb index based on ev-degree.**

From Table 3 we compute the Zagreb index based on ev-degree:

$$M^{ev}(\mathcal{G}) = \sum_{e\in E(\mathcal{G})} \Lambda_{ev}(e)^2,$$
$$M^{ev}(\mathcal{G}) = (3)^2(4n+1) + (4)^2(5n+1) + (4)^2(12n) + (5)^2(25n) + (6)^2(10n)$$
$$= 1293n + 25.$$

- **The first Zagreb α-index based on *ve*-degree.**

From Table 4 we compute the first Zagreb α-index based on *ve*-degree:

$$M_1^{\alpha ve}(\mathcal{G}) = \sum_{v\in V(\mathcal{G})} \Lambda_{ve}(v)^2,$$
$$M_1^{\alpha ve}(\mathcal{G}) = (2)^2(4n+1) + (3)^2(5n+1) + (3)^2(n) + (4)^2(9n+1) + (5)^2(11n)$$
$$+(6)^2(6n-1) + (5)^2(3n) + (6)^2(n) + (7)^2(8n+1) + (8)^2(5n-1)$$
$$= 1528n - 22.$$

- **The first Zagreb β-index based on *ve*-degree.**

From Table 5 we compute the first Zagreb β-index based on *ve*-degree:

$$M_1^{\beta ve}(\mathcal{G}) = \sum_{uv\in E(\mathcal{G})} (\Lambda_{ve}(u) + \Lambda_{ve}(v)),$$
$$M_1^{\beta ve}(\mathcal{G}) = (5)(1) + (6)(4n) + (7)(3n) + (10)(2n+1) + (7)(n) + (8)(n) + (9)(9n)$$
$$+(10)(n) + (10)(n) + (11)(2n+1) + (10)(4n) + (11)(2n) + (12)(2n) + (13)(3n)$$
$$+(11)(2n) + (13)(8n-1) + (14)(n) + (14)(2) + (15)(10n-2)$$
$$= 618n + 11.$$

- **The second Zagreb index based on *ve*-degree.**

From Table 5 we compute The second Zagreb index based on *ve*-degree:

$$M_2^{ve}(\mathcal{G}) = \sum_{uv\in E(\mathcal{G})} (\Lambda_{ve}(u)\Lambda_{ve}(v)),$$
$$M_2^{ve}(\mathcal{G}) = (6)(1) + (8)(4n) + (15)(3n) + (21)(2n+1) + (12)(n) + (16)(n) + (20)(9n)$$
$$+(25)(n) + (24)(n) + (28)(2n+1) + (25)(4n) + (30)(2n) + (35)(2n) + (40)(3n)$$
$$+(30)(2n) + (42)(8n-1) + (48)(n) + (49)(2) + (56)(10n-2)$$
$$= 3193m - 46.$$

- **The Randic index based on *ve*-degree.**

From Table 5 we compute The Randic index based on *ve*-degree:

$$R^{ve}(\mathcal{G}) = \sum_{uv\in E(\mathcal{G})} (\Lambda_{ve}(u)\Lambda_{ve}(v))^{-\frac{1}{2}},$$
$$R^{ve}(\mathcal{G}) = (6)^{-\frac{1}{2}}(1) + (8)^{-\frac{1}{2}}(4n) + (15)^{-\frac{1}{2}}(3n) + (21)^{-\frac{1}{2}}(2n+1) + (12)^{-\frac{1}{2}}(n) + (16)^{-\frac{1}{2}}(n)$$
$$+(20)^{-\frac{1}{2}}(9n) + (25)^{-\frac{1}{2}}(n) + (24)^{-\frac{1}{2}}(n) + (28)^{-\frac{1}{2}}(2n+1) + (25)^{-\frac{1}{2}}(4n) + (30)^{-\frac{1}{2}}(2n)$$
$$+(35)^{-\frac{1}{2}}(2n) + (40)^{-\frac{1}{2}}(3n) + (30)^{-\frac{1}{2}}(2n) + (42)^{-\frac{1}{2}}(8n-1) + (48)^{-\frac{1}{2}}(n) + (49)^{-\frac{1}{2}}(2) + (56)^{-\frac{1}{2}}(10n-2)$$
$$= \left(\frac{5}{4} + \sqrt{2} + \frac{\sqrt{15}}{5} + \frac{2}{\sqrt{21}} + \frac{\sqrt{3}}{4} + \frac{9\sqrt{5}}{10} + \frac{\sqrt{6}}{12} + \frac{1}{\sqrt{7}} + \frac{2\sqrt{30}}{15} + \frac{2}{\sqrt{35}} + \frac{3\sqrt{10}}{20} + \frac{4\sqrt{42}}{21} + \frac{5\sqrt{14}}{14}\right)n$$
$$+\frac{2}{7} + \frac{1}{\sqrt{6}} + \frac{1}{\sqrt{21}} + \frac{\sqrt{7}}{14} - \frac{1}{\sqrt{42}} - \frac{1}{\sqrt{14}}.$$

Table 4. Ve-degrees partition.

$deg(u)$	ve-degree	Frequency
1	2	$4n+1$
1	3	$5n+1$
2	3	n
2	4	$9n+1$
2	5	$11n$
2	6	$6n-1$
3	5	$3n$
3	6	n
3	7	$8n+1$
3	8	$5n-1$

Table 5. End vertices edge partitions based on ve degree.

$(deg(u), d(v))$	*ve*-degree	Frequency
(2, 1)	(3, 2)	1
(2, 1)	(4, 2)	$4n$
(3, 1)	(5, 3)	$3n$
(3, 1)	(7, 3)	$2n+1$
(2, 2)	(4, 3)	n
(2, 2)	(4, 4)	n
(2, 2)	(5, 4)	$9n$
(2, 2)	(5, 5)	n
(3, 2)	(6, 4)	n
(3, 2)	(7, 4)	$2n+1$
(3, 2)	(5, 5)	$4n$
(3, 2)	(6, 5)	$2n$
(3, 2)	(7, 5)	$2n$
(3, 2)	(8, 5)	$3n$
(3, 2)	(5, 6)	$2n$
(3, 2)	(7, 6)	$8n-1$
(3, 2)	(8, 6)	n
(3, 3)	(7, 7)	2
(3, 3)	(8, 7)	$10n-2$

- **The Randic index based on *ev*-degree.**

From Table 3 we compute The Randic index based on *ev*-degree:

$$R^{ev}(\mathcal{G}) = \sum_{e\in E(\mathcal{G})} \Lambda_{ev}(e)^{-\frac{1}{2}},$$

$$R^{ev}(\mathcal{G}) = (3)^{-\frac{1}{2}}(4n+1) + (4)^{-\frac{1}{2}}(5n+1) + (4)^{-\frac{1}{2}}(12n) + (5)^{-\frac{1}{2}}(25n) + (6)^{-\frac{1}{2}}(10n)$$

$$= \left(\frac{17}{2} + \frac{4}{\sqrt{3}} + 5\sqrt{5} + \frac{5\sqrt{6}}{3}\right)n + \frac{1}{2} + \frac{1}{\sqrt{3}}.$$

- **The atom-bond connectivity index based on *ve*-degree.**

From Table 5 we compute The atom-bond connectivity index based on *ve*-degree:

$$ABC^{ve}(\mathcal{G}) = \sum_{uv\in E(\mathcal{G})} \sqrt{\frac{\Lambda_{ve}(u)+\Lambda_{ve}(v)-2}{(\Lambda_{ve}(u)\Lambda_{ve}(v))}},$$

$$ABC^{ve}(\mathcal{G}) = \sqrt{\frac{3}{6}}(1) + \sqrt{\frac{4}{8}}(4n) + \sqrt{\frac{5}{15}}(3n) + \sqrt{\frac{8}{21}}(2n+1) + \sqrt{\frac{5}{12}}(n) + \sqrt{\frac{6}{16}}(n) + \sqrt{\frac{7}{20}}(9n)$$
$$+\sqrt{\frac{8}{25}}(n) + \sqrt{\frac{8}{24}}(n) + \sqrt{\frac{9}{28}}(2n+1) + \sqrt{\frac{8}{25}}(4n) + \sqrt{\frac{9}{30}}(2n) + \sqrt{\frac{10}{35}}(2n) + \sqrt{\frac{11}{40}}(3n)$$
$$+\sqrt{\frac{9}{30}}(2n) + \sqrt{\frac{11}{42}}(8n-1) + \sqrt{\frac{12}{48}}(n) + \sqrt{\frac{12}{49}}(2) + \sqrt{\frac{13}{56}}(10n-2)$$
$$= \left(\frac{1}{2} + 4\sqrt{2} + \frac{4}{\sqrt{3}} + \frac{4\sqrt{42}}{21} + \frac{\sqrt{15}}{6} + \frac{\sqrt{6}}{4} + \frac{9\sqrt{35}}{10} + \frac{3}{\sqrt{7}} + \frac{2\sqrt{30}}{5} + \frac{2\sqrt{14}}{7}\right.$$
$$\left. + \frac{3\sqrt{110}}{20} + \frac{4\sqrt{462}}{21} + \frac{5\sqrt{182}}{14}\right)n + \frac{1}{\sqrt{2}} + \frac{2\sqrt{42}}{21} + \frac{3\sqrt{7}}{14} - \frac{\sqrt{462}}{42} + \frac{4\sqrt{3}}{7} - \frac{\sqrt{182}}{14}.$$

- **The goemetric-arithmetic index based on *ve*-degree.**

From Table 5 we compute the goemetric-arithmetic index based on *ve*-degree:

$$GA^{ve}(\mathcal{G}) = \sum_{uv\in E(\mathcal{G})} \frac{2\sqrt{\Lambda_{ve}(u)\times\Lambda_{ve}(v)}}{(\Lambda_{ve}(u)+\Lambda_{ve}(v))},$$

$$\begin{aligned}GA^{ve}(\mathcal{G}) &= \frac{2\sqrt{6}}{5}(1)+\frac{2\sqrt{8}}{4}(4n)+\frac{2\sqrt{15}}{7}(3n)+\frac{2\sqrt{21}}{10}(2n+1)+\frac{2\sqrt{12}}{7}(n)+\frac{2\sqrt{16}}{8}(n)\\ &+\frac{2\sqrt{20}}{9}(9n)+\frac{2\sqrt{25}}{10}(n)+\frac{2\sqrt{24}}{10}(n)+\frac{2\sqrt{28}}{11}(2n+1)+\frac{2\sqrt{25}}{10}(4n)+\frac{2\sqrt{30}}{11}(2n)\\ &+\frac{2\sqrt{35}}{12}(2n)+\frac{2\sqrt{40}}{13}(3n)+\frac{2\sqrt{30}}{11}(2n)+\frac{2\sqrt{42}}{13}(8n-1)+\frac{2\sqrt{48}}{14}(n)\\ &+\frac{2\sqrt{49}}{14}(2)+\frac{2\sqrt{56}}{15}(10n-2)\\ &=\Bigg(6+4\sqrt{2}+4\sqrt{5}+\frac{6\sqrt{15}}{7}+\frac{2\sqrt{21}}{5}+\frac{8\sqrt{3}}{7}+\frac{2\sqrt{6}}{5}+\frac{8\sqrt{7}}{11}+\frac{8\sqrt{30}}{11}+\frac{\sqrt{35}}{3}+\frac{12\sqrt{10}}{13}\\ &\quad+\frac{16\sqrt{42}}{13}+\frac{8\sqrt{14}}{3}\Bigg)n+2+\frac{2\sqrt{6}}{5}+\frac{\sqrt{21}}{5}+\frac{4\sqrt{7}}{11}-\frac{2\sqrt{42}}{13}-\frac{8\sqrt{14}}{15}.\end{aligned}$$

- **The harmonic index based on *ve*-degree.**

From Table 5 we compute the harmonic index based on *ve*-degree:

$$H^{ve}(\mathcal{G}) = \sum_{uv\in E(\mathcal{G})} \frac{2}{\Lambda_{ve}(u)+\Lambda_{ve}(v)},$$

$$\begin{aligned}H^{ve}(\mathcal{G}) &= \frac{2}{5}(1)+\frac{2}{6}(4n)+\frac{2}{7}(3n)+\frac{2}{10}(2n+1)+\frac{2}{7}(n)+\frac{2}{8}(n)+\frac{2}{9}(9n)\\ &+\frac{2}{10}(n)+\frac{2}{10}(n)+\frac{2}{11}(2n+1)+\frac{2}{10}(4n)+\frac{2}{11}(2n)+\frac{2}{12}(2n)+\frac{2}{13}(3n)\\ &+\frac{2}{11}(2n)+\frac{2}{13}(8n-1)+\frac{2}{14}(n)+\frac{2}{14}(2)+\frac{2}{15}(10n-2)\\ &=\frac{218597}{20020}n+\frac{1943}{3003}.\end{aligned}$$

- **The sum-connectivity index based on *ve*-degree.**

From Table 5 we compute the sum-connectivity index based on *ve*-degree:

$$\chi^{ve}(\mathcal{G}) = \sum_{uv\in E(\mathcal{G})} (\Lambda_{ve}(u)+\Lambda_{ve}(v))^{-\frac{1}{2}},$$

$$\begin{aligned}\chi^{ve}(\mathcal{G}) &= (5)^{-\frac{1}{2}}(1)+(6)^{-\frac{1}{2}}(4n)+(7)^{-\frac{1}{2}}(3n)+(10)^{-\frac{1}{2}}(2n+1)+(7)^{-\frac{1}{2}}(n)+(8)^{-\frac{1}{2}}(n)\\ &+(9)^{-\frac{1}{2}}(9n)+(10)^{-\frac{1}{2}}(n)+(10)^{-\frac{1}{2}}(n)+(11)^{-\frac{1}{2}}(2n+1)+(10)^{-\frac{1}{2}}(4n)+(11)^{-\frac{1}{2}}(2n)\\ &+(12)^{-\frac{1}{2}}(2n)+(13)^{-\frac{1}{2}}(3n)+(11)^{-\frac{1}{2}}(2n)+(13)^{-\frac{1}{2}}(8n-1)+(14)^{-\frac{1}{2}}(n)\\ &+(14)^{-\frac{1}{2}}(2)+(15)^{-\frac{1}{2}}(10n-2)\\ &=\left(\frac{2\sqrt{6}}{3}+\frac{4}{\sqrt{7}}+\frac{4\sqrt{10}}{5}+\frac{\sqrt{2}}{4}+3+\frac{6\sqrt{11}}{11}+\frac{1}{\sqrt{3}}+\frac{11}{\sqrt{13}}+\frac{1}{\sqrt{14}}+\frac{2\sqrt{15}}{3}\right)n\\ &+\frac{1}{\sqrt{5}}+\frac{1}{\sqrt{10}}+\frac{1}{\sqrt{11}}-\frac{1}{\sqrt{13}}+\frac{\sqrt{14}}{7}-\frac{2}{\sqrt{15}}.\end{aligned}$$

Table 6. Numerical values of the computed Ev and Ve-degree based indices.

$[m]$	[1]	[2]	[3]	[4]	[5]	[6]	[7]	[8]	[9]	[10]
$\mathbf{M}^{ev}$	1318	2611	3904	5197	6490	7783	9076	10369	11662	12955
$\mathbf{M}_1^{\alpha ve}$	1506	3034	4562	6090	7618	9146	10674	12202	13730	15258
$\mathbf{M}_1^{\beta ve}$	629	1247	1865	2483	3101	3719	4337	4955	5573	6191
$\mathbf{M}_2^{ve}$	1785	3571	5357	7143	8929	10715	12501	14287	16073	17859
$\mathbf{R}^{ve}$	11.69	22.71	33.73	44.74	55.76	66.78	77.79	88.81	99.83	110.84
$\mathbf{R}^{ev}$	27.15	53.22	79.29	105.37	131.44	157.51	183.58	209.66	235.73	261.79
$\mathbf{ABC}^{ve}$	32.57	63.73	94.89	126.05	157.22	188.38	219.54	250.70	281.87	313.03
$\mathbf{GA}^{ve}$	59.33	116.79	174.26	231.73	289.19	346.66	404.13	461.59	519.06	576.52
$\mathbf{H}^{ve}$	11.57	22.48	33.40	44.32	55.24	66.16	77.08	87.99	98.92	109.84
$\boldsymbol{\chi}^{ve}$	18.12	35.44	52.75	70.06	87.38	104.69	122.01	139.32	156.64	173.95

5. Numerical comparison and analysis

Topological indices based QSAR models can play a significant role in reducing the expense of time, human services, physical facilities and animal studies to discover drugs or drug targets. The QSAR models based descriptor particularly used to understand the biological behavior of anti-parasite medications that are being researched in significant part. Correlation of degree-based topological descriptor occurring in chemical literature has been verified for generic heat forming and usual octane isomer boiling points. The association capacity of each of these indexes is considered to be either very low or zero. In this portion, we have provided numerical results for *ev*-degree and *ve*-degree related topological descriptors for the structure of Hydroxyethyl starch conjugated with Hydroxychloroquine (HCQ-HEC) to understand the similarities between statistical and biological behavior. We have used different values of n to compute numerical tables for the ev-degree and ve-degree based indices such as the Zagreb (M^{ev}) and the Randic (R^{ev}) indexes based on *ev*-degree, first Zagreb α-index ($M_1^{\alpha ve}$), first Zagreb β-index ($M_1^{\beta ve}$), Randic index (R^{ve}), second Zagreb index (M_2^{ve}), atom-bond connectivity (ABC^{ve}) index, harmonic (H^{ve}) index, geometric-arithmetic (GA^{ve}) index and sum-connectivity (χ^{ve}) index based on *ve*-degrees to predict physiochemical and medication properties for the molecular structure of (HCQ-HES), (see Tables 6). Moreover, we have drawn the graphs 3-7 for the structure of (HCQ-HES) to review the behavior of topological descriptors computed above to predict the level of toxicity, antidotes, physiochemical and medication properties of drugs. We have provided the comparison graphs related to M^{ev}, $M_1^{\alpha ve}$, $M_1^{\beta ve}$ and M_2^{ve} given in Figure 8(a) and graph related to R^{ve}, R^{ev}, ABC^{ve}, GA^{ve}, H^{ve} and χ^{ve} given in Figure 8(b). We also provide all indices comparison result by graphical representation see Figure 9

It can be observed from the Figures 3–7 and Table 6 that all topological descriptors computed for the structures of (HCQ-HES) increases with the increase in n.

For the computation of the overall π-electronic energy of the molecules, the Zagreb form indices were found;[48] thus, in the case of (HCQ-HES) for higher values of n, the π-electronic energy is growing/increases.

In studying the chemical similarity of molecular compounds, the Randic index can be used, which necessary to allow for the automatic decision making.[49] The Randic index is among the most commonly employed molecular-graphic structure descriptors and is surprising to note that its alteration functions considerably better than the normal version. In addition, the Randic index used for the calculation of the Kovat constants and the boiling point of the compounds. The Randic index for the molecular structure of (HCQ-HES) increases by the increment in n.

The predictive power of the geometric-arithmetic index was found to be superior to that of the Randic connectivity index. With the rise in n, the GA index for (HCQ-HES) structure is increases.

The Atomic Bond Connectivity (ABC) index presents a very strong correlation for calculating cycloalkanes strain energy and also for the stability of linear and branched alkanes.[50] The ABC index for the (HCQ-HES) increases with increment in n. In the current research, the ABC index

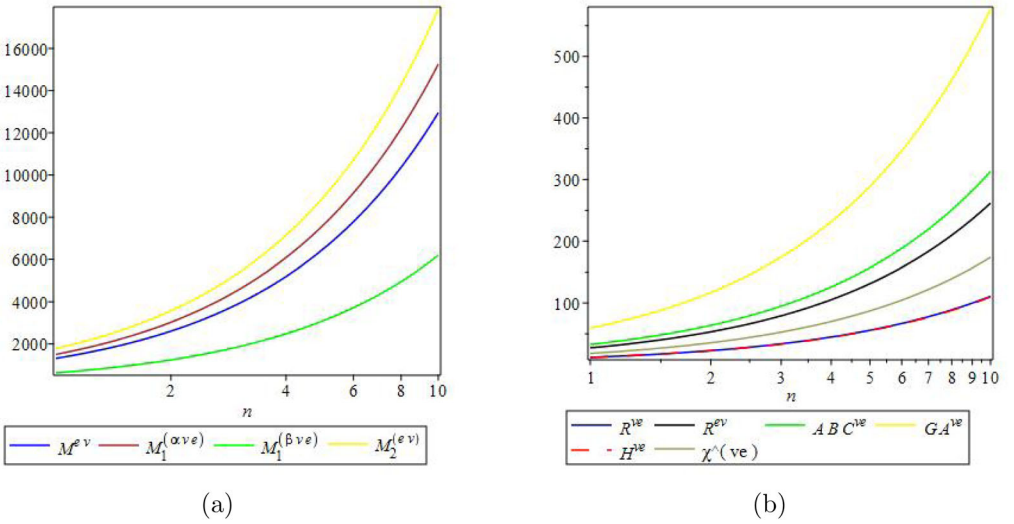


Figure 8. Comparison of all indices.

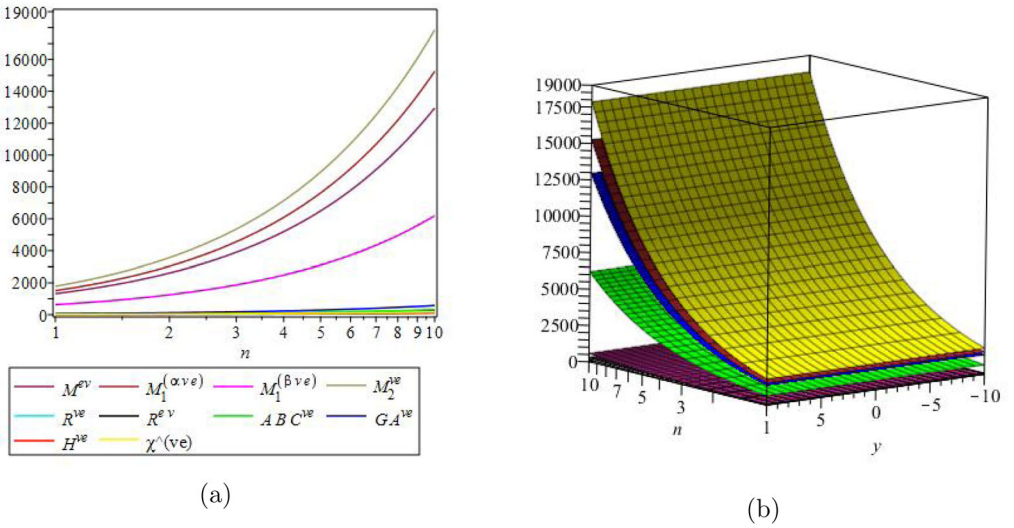


Figure 9. Comparison of all indices.

increases for the structure of (HCQ-HES) with the enhancement of *n*. The Zagreb index and the atom-bond connectivity index show the better results. Also the ev-degree Randic index and Harmonic index are correlated (see Figure 8(b)).

The recently introduced sum-connectivity index and harmonic index, while they have fairly strong correlation capacities, are outperformed than any of the older indices. The rationale for their usage in quantitative structural–property relationship/quantitative structure-activity relationship (QSPR/QSAR) is thus unclear.

6. Application

The Topological Indices Technique has opened up a broad variety of potential uses for the assessment of QSAR antiparasitic products. Topological indices used to research network topologies

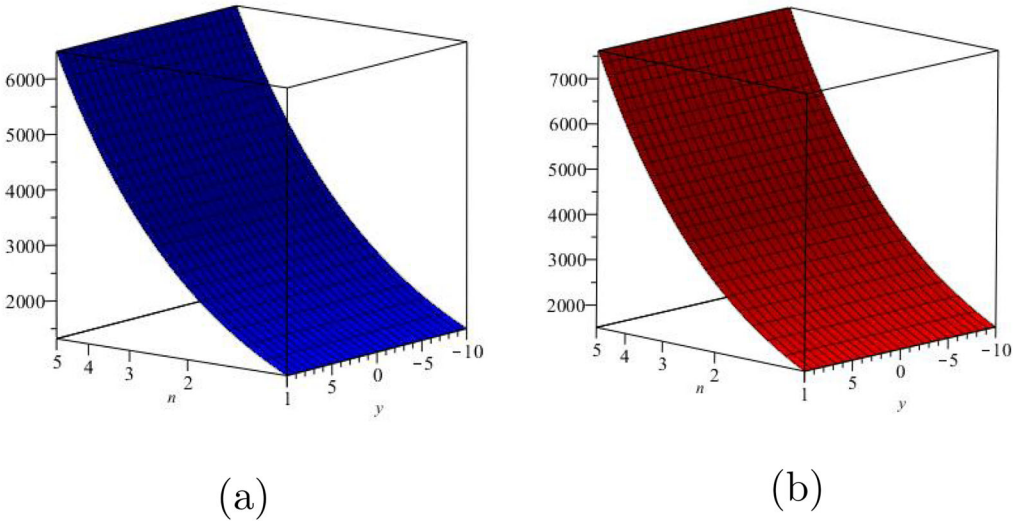


Figure 3. (a) The Zagreb index based on *ev*-degree, (b) The first Zagreb α-index based on *ve*-degree.

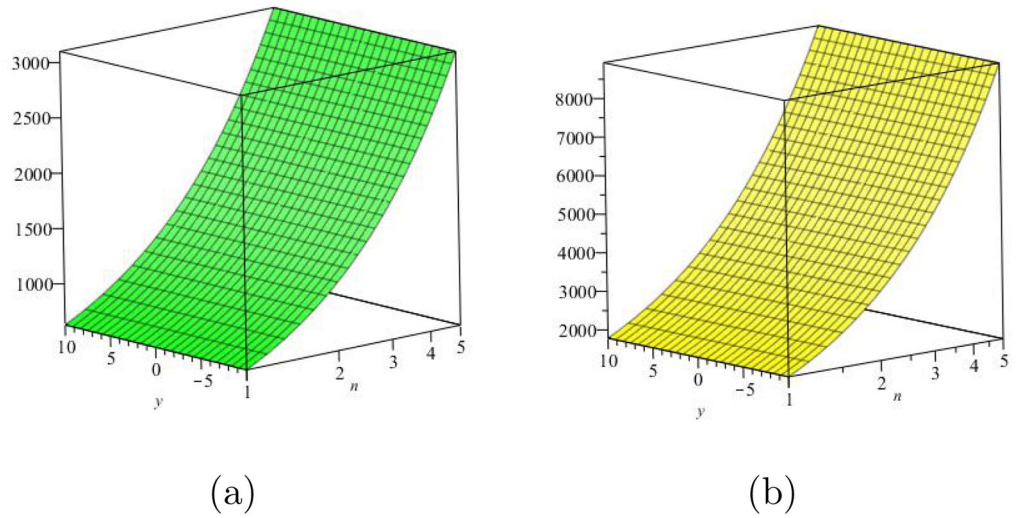


Figure 4. (a) The first Zagreb β-index based on *ve*-degree, (b) The second Zagreb index based on *ve*-degree.

have offered different possibilities for the identification of drug targets for parasite disease. Current QSAR studies are expected to be applied to complex issues, including the design of anti-parasite drugs and the development of drug targets. The usage of technology and QSAR models in drug development analysis and medicinal chemistry has been growing in recent times. Quantitative Structure-Activity Relationship (QSAR) frameworks of Medicinal Chemistry and Pharmaceutical design are used for the development of anti-parasite medicines. Since the COVID-19 is the novel major issue of the world with continuously increasing the ratio of cases and death. Effective treatment for this COVID-19 pandemic is an essential aspect of current medical research. Chloroquine and hydroxychloroquine are a couple of old drugs used for malaria prevention and recovery are permitting for the treatment of COVID-19 in case of emergency. Studies released in February and March indicate that medications suppress the virus that triggers

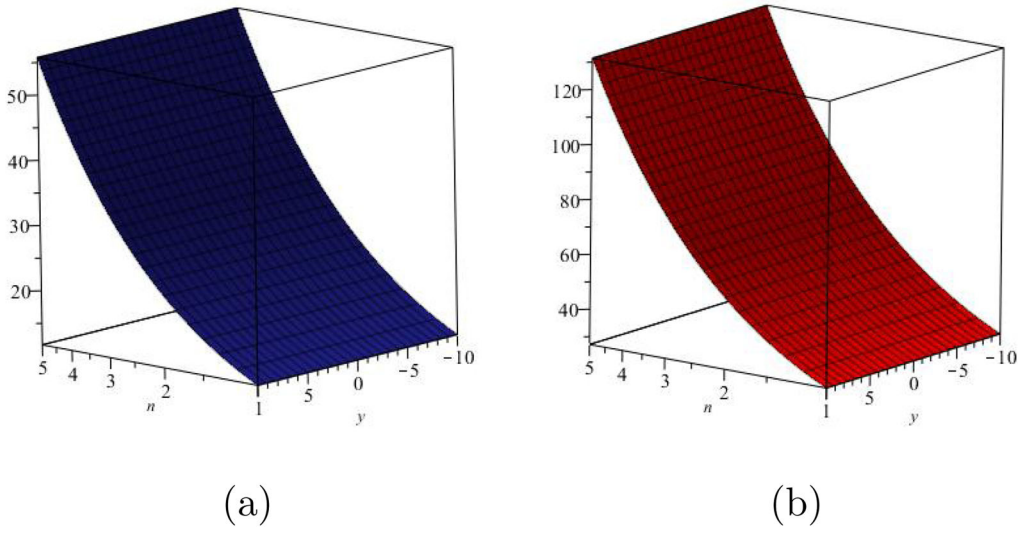


Figure 5. (a) The Randic index based on *ve*-degree, (b) The Randic index based on *ev*-degree.

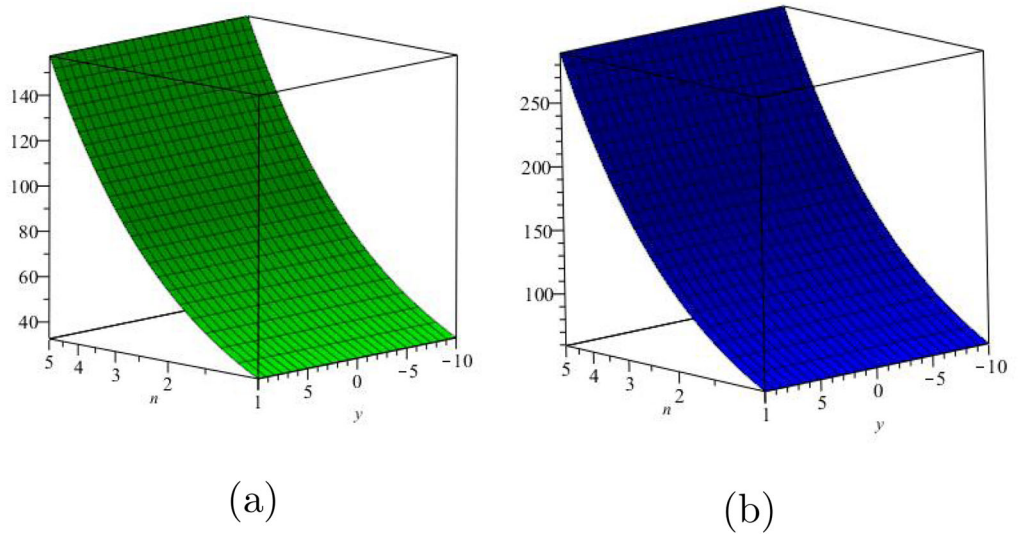


Figure 6. (a) The atom-bond connectivity index based on *ve*-degree, (b) The goemetric-arithmetic index based on *ve*-degree.

COVID-19 in monkey cells. A limited clinical experiment in France revealed that hydroxychloroquine helps people recover more rapidly from the infection, although another experimental test in Beijing showed no significant advantage to this medication. Many clinical studies, including one funded by the World Health Organization, are planned to carry out more stringent research on the medicines.

Chloroquine has emerged regularly over the past decade as a possible antiviral against developing pathogens. Research in 2004 and 2005 also established it as an agent of the initial coronavirus SARS. Scientists have since conducted several studies using chloroquine or hydroxychloroquine to prevent or reduce viral infections in mice, including OC43 coronavirus, avian influenza, Ebola virus, Zika virus, and MERS-CoV – the coronavirus that causes respiratory syndrome in the Middle East. However, human studies were less successful, and the drugs were never approved

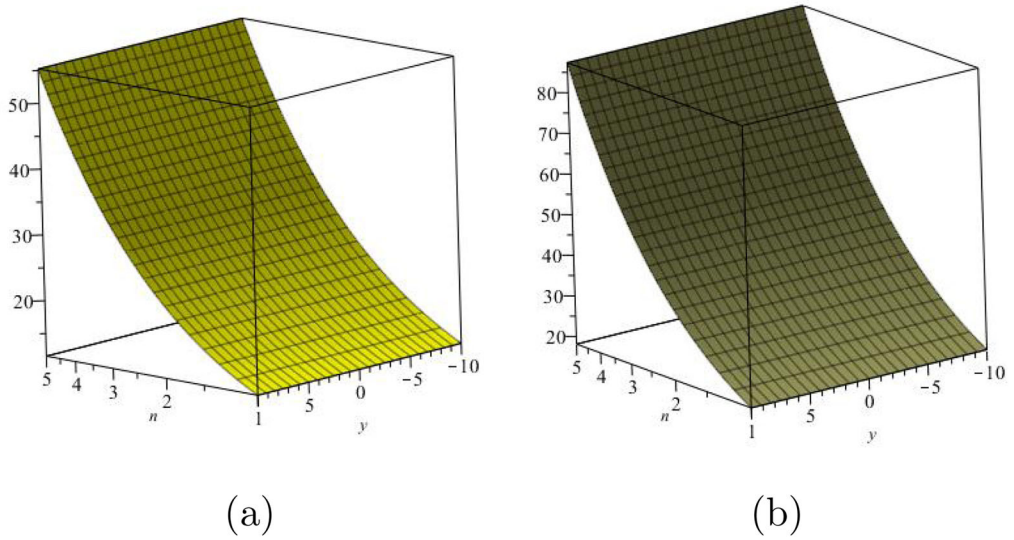


Figure 7. (a) The harmonic index based on *ve*-degree, (b) The sum-connectivity index based on *ve*-degree.

for the treatment of viral infections. Despite the absence of clear data in patients, many drug companies have promised to donate millions of doses in the months ahead. Hydroxychloroquine or chloroquine, sometimes in conjunction with second-generation macrolide, is commonly used for the diagnosis of COVID-19, without definitive proof of its benefit. Coupling a cytotoxic drug to a macromolecular product increases a drug's pharmacokinetic profile, prolongs the delivery of medicines and reduces time.[51,52]

7. Conclusion

Topological indices methodology has opened up a broad variety of possible applications for the QSAR estimation of antiparasitic drugs. Topological indices used to study network topologies which have provided new possibilities for detecting drug targets in parasites disease. It is expected that current QSAR studies will be applied in complicated problems including the design of anti-parasite drugs and the development of drug targets. To understand and then analyzing the underlying topologies through topological descriptors is important. These experimental studies have a broad range of applications in the fields of chem-informatics, bio-informatics and bio-medicine, where various graph topological based assessments are used to tackle many complicated schemes. Graphs topologies are important tools for approximating and predicting the properties of biological and chemical compounds in the analysis of the quantitative structure-property relationships (QSPRs) and the quantitative structure-activity relationships (QSARs). In this paper, we provided results related to the ev-degree and ve-degree based topological indices such as the Zagreb (M^{ev}) and the Randic (R^{ev}) indexes based on *ev*-degree, first Zagreb α-index ($M_1^{\alpha ve}$), first Zagreb β-index ($M_1^{\beta ve}$), Randic index (R^{ve}), second Zagreb index (M_2^{ve}), atom-bond connectivity (ABC^{ve}) index, harmonic (H^{ve}) index, geometric-arithmetic (GA^{ve}) index and sum-connectivity (χ^{ve}) index based on *ve*-degrees for molecular structure of Hydroxyethyl starch conjugated with Hydroxychloroquine (HCQ-HEC) to study the pharmaceutical properties of drugs. All the topological descriptor are in increasing order.

Disclosure statement

There are no conflicts of interest.

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