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Dedicated to Professor Zeno Simon
on the occasion of his 80th anniversary

THEORETICAL INVESTIGATIONS OF QUERCETIN AND ITS ANALOGUES AS ANTICANCER AGENTS**

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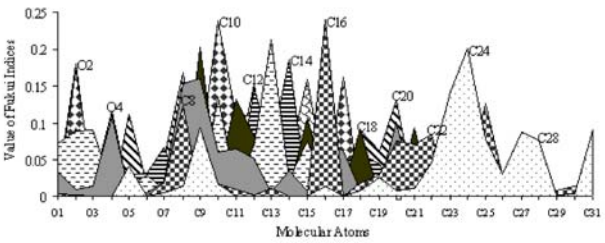
In search for anticancer drugs, numerous laboratory studies and human clinical trials showed that flavonoids have important effects on cancer chemoprevention and chemotherapy. Flavonoids have been considered as mapping agents to guide the development of small molecule probes for enzyme catalytic sites which establish key structural features for potent and potentially selective inhibition. It is well known that small chemical modifications on the flavonoid core can have significant effects on the activity. In this light, we investigated, theoretically, the structural and electronic properties of quercetin, narigenin, luteolin, galangin and vitexin derivatives by performing semiempirical molecular orbital theory at the level AM1 and density functional theory quantum chemical calculations. Additionally to the electronic molecular properties (heat of formation, HOMO and LUMO energies, molecular electrostatic potential, and atomic Fukui indices), we discuss pharmacokinetical aspects of these compounds. Understanding the chemical behavior natural flavonoids may assist decision-making in medical chemistry.



INTRODUCTION

Flavonoids are a group of over 9,000 naturally compounds widely distributed in the plant kingdom, and commonly found in fruit, vegetables, nuts, seeds, stems, flowers, tea, wine, propolis and honey providing color and flavors.[1,2] Progressively, flavonoids have become an important subject for medical research. They possess a remarkable array of biological properties including anti-oxidative, tissue-protective, radical scavenging, anti-inflammatory, anti-diabetic, hepatoprotective, capillary strengthening, and anti-cancer effects.[3-7] All phenolic derivatives are unstable and undergo various enzymatic and chemical reactions (*e.g.* during food processing). To date, laboratory data

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studies, epidemiological investigations, and human clinical trials indicate that flavonoids have important effects on cancer chemoprevention and chemotherapy.[8-10] In vitro studies have indicated considerable differences in the anti-oxidative potential, bioavailability, distribution, and metabolism of different flavonoid subgroups, depending on their chemical structures. Because of these differences, flavonoid compounds may have different effects on human health.[11,12]

These remarks provoked considerable interest to evaluate the key functional groups on the flavonoid structure which influence the activity and the ADME (absorption, distribution, metabolism, and excretion) profile. Flavonoids share a common structure of two or more aromatics rings (the A and B rings) connected by a third pyranic ring (the C ring), (Fig. 1). Based on the variation to the heterocyclic C-ring, flavonoids are divided into six major subclasses including flavones (*e.g.*, apigenin, luteolin), flavonols (*e.g.*, quercetin, fisetin), flavonones (*e.g.*, narigenin, hespertin), catechins (*e.g.*, catechin), anthocyanidins (*e.g.*, pelargonidin, malvidin) and isoflavones (*e.g.*, daidzein, genistein).[13,14] Flavonoids such as luteolin, flavopiridol, fisetin, or the common dietary flavonol, quercetin, are the most widely investigated compounds which display anticancer, anti-oxidant and anti-inflammatory effects.[15,16] Some of them have already entered in clinical trials.[17,18] Owing to flavonoids importance in human health and their structural diversity, a better understanding of their structures, their reactivity and chemical properties in addition to the mechanisms generating them appears essential to create new chemotherapeutic agents with improved physicochemical profile. In this regard, computational chemistry together with experimental information, play an important role to guide and speed up this process. Despite the numerous investigations on flavone, flavonols and flavonone classes, only few computational studies have been reported to date on quercetin, luteolin, narigenin, galangin and vitexin. Some of these computational investigations were made only at low theory level (*e.g.* Austin Model 1 - AM1).[19,20] For this reason, the further investigation using high theory level methods is important. Herein, we have selected quercetin (**1**), naringenin (**2**), luteolin (**3**), galangin (**4**) and vitexin (**5**) (Fig. 1) owing to their distinct chemical features, in order to throw light on their structural properties through semiempirical AM1 and density functional theory (DFT) quantum chemical calculations. Those methods provide a good balance between qualities of results, price and computational time.[21-23] Theoretical values are compared with each other among the five flavonoids in order to discuss the effect of the various molecular features. Additionally to the electronic molecular properties, the Lipinski's rule of five and ADMET parameters were calculated as complementary indicators to the final clinical success of a drug candidate. Electronic properties and ADME profile of flavonoids developed by theoretical calculation methods can contribute to a better understanding of the flavonoid structures for a better exploitation in the field of chemistry, biology and food sciences.

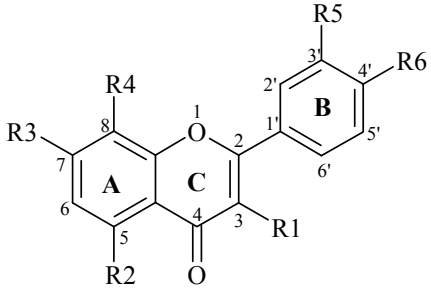
MATERIAL AND METHODS

Computational details

The five flavonoid structures (Fig. 1) were built and preoptimized with molecular mechanic force field (MM+) and semi-empirical AM1 methods using the HyperChem software.[24] Geometry optimization was carried out by using the Polak-Ribere algorithm with the SCF convergence set to 0.0001 kcal/mol and the RMS gradient set to 0.001 kcal/(Åmol). These methods ease full optimization by extended methods. Therefore we carried out complete optimization of the AM1 preoptimized structures by applying hybrid DFT with B3LYP (Becke, three-parameter, Lee-Yang-Parr) exchange-correlation functional and using the basis set 6-31G(d,p) level to calculate the electronic properties of the titled compounds. The electronic properties, *e.g.*, heat of formation, HOMO and LUMO energies, atomic Fukui indices, and molecular electrostatic potential (ESP) were computed using Jaguar module of Schrodinger package.[25] The outlines of the calculated quantum chemical properties provide additional mechanistic information about the activity of these analogues.

Electronic parameters

Heat of formation (ΔH_f^θ) is the energy released or absorbed as heat when 1 mol of a compound is formed by combination of its elements in their standard states (*i.e.* T=298.15K and P=1atm). ΔH_f^θ is an important indicator regarding the thermodynamic stability or instability of compound. Compounds with high negative values of heats of formation are very stable, and those with slightly negative or positive values, are relatively unstable and may react or spontaneously decompose into their elements.[26]



(1) R1, R2, R3, R5, R6 = -OH; R4= -H
(2) R2, R3, R6 = -OH; R1, R4, R5= -H, C2-C3 single bond
(3) R2, R3, R5, R6 = -OH; R1, R4= -H
(4) R1, R2, R3 = -OH; R4, R5, R6 = -H
(5) R2, R3, R6 = -OH; R1, R5= -H; R4= galactose

Fig. 1 – Structures of quercetin (**1**), naringenin (**2**), luteolin (**3**), galangin (**4**), and vitexin (**5**).

HOMO and LUMO orbitals. The highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO), sometimes referred to as frontier orbitals, play an important role in the chemical reactivity of a molecule. The locations of the HOMO and LUMO indicate the sites of a nucleophilic or electrophilic attack. The electron-donating or electron-affinity capability of a molecule can be determined by the values of HOMO or LUMO. A high HOMO values correspond to a strong capability to donate electrons and characterize the susceptibility of the molecule toward attack by electrophiles. The energy of the LUMO is related to the electron affinity and describes the susceptibility of the molecule toward attack by nucleophiles.[27,28] The LUMO-HOMO gap (ΔE) calculated as the difference of the energies between the HOMO and LUMO orbitals is an important stability and chemical reactivity index. A large ΔE implies high stability for the molecule and lower reactivity in chemical reactions whereas a small ΔE suppose low stability and higher molecular reactivity.[29,30]

Atomic Fukui indices – or reactivity indices provide information about which atoms in a molecule have a larger tendency to either loose or accept an electron. Shortly, reactivity indices specify which atoms in a molecule are more likely to undergo a nucleophilic or an electrophilic attack. Fukui indices contain two subscripts N (f_NN) or S (F_SS) corresponding to the electron density or the spin density, respectively. A high positive value of f_NN for HOMO indicates the atom that is the most reactive towards electrophilic attacks (nucleophilic agent) and a high positive value of f_NN for LUMO indicates the atom that is the most reactive towards nucleophilic attacks (electrophilic agent).[31,32]

Electrostatic potential (**ESP**) – can be defined simply as the difference in electrical charge between two points. ESP is considered as an effective tool for interpreting, predicting and improving the molecular reactive behavior. Several applications of ESP are (i) the prediction of molecule regions susceptible to nucleophilic or electrophilic attack, (ii) the prediction of mutagenic potential and chemical carcinogenesis of molecules, (iii) in maintaining the structural properties of proteins and nucleic acids.[33] Positively charged species (electrophiles) tend to be attracted in regions of the molecules corresponding to the most negative ESP values whereas the negatively charged species (nucleophiles) are attracted in areas of the molecules where the ESP has the most positive values.[31,34,35] The best way to evaluate these data is to visually represent it, as an electrostatic potential map. The main purpose of electrostatic potential maps is to illustrate the partial charge distribution of a molecule. In order to easily interpret the ESP data, a color code, with red as the lowest electrostatic potential value and blue as the highest, is employed. The HOMO and LUMO orbitals, Fukui indices, charge distribution as well as ESP of all five structures were visualized with Maestro module of Schrodinger.[36]

Lipinski rule of five and ADME profiles. The ADME profile of quercetin and their analogues was predicted using QikProp module of Schrodinger package.[37] In the present study, QikProp properties such as molecular weight (MW), QPlogPo/w, QPlogS, QPlogHERG, QPPCaco, QPlogBB, percent human oral absorption, and PSA were computed to obtain the ADME properties (Table 3).[37]Additionally, we calculated the compliance of analogues to the Lipinski's rule of five (LRo5). This rule assumes that a compound is more likely to be membrane permeable and easily absorbed by the body if it matches the following criteria: molecular weight <500, lipophilicity (logP) <5, hydrogen bond donor (HBD) <5 and hydrogen bond acceptor (HBA)<10.[38-42] Topological polar surface area (TPSA <130Å^2) as another drug bioavailability

indicator was computed.[43] Molecules violating more then one of these rules may have bioavailability problems.

RESULTS AND DISCUSSION

In this part of the manuscript, the electronic features of the five flavonoids obtained through AM1 and DFT calculations are presented and analyzed in conjunction with the ADME predictions.

Electronic parameters. The HOMO and LUMO frontier orbital calculated for the five flavonoid compounds at the B3LYP/6-31G** level are drawn in Fig. 2 and the frontier orbital energies are also shown in Table 1. Looking at Fig. 2, it can be observed that the HOMO frontier orbitals of the four flavonoid compounds (**1**, **2**, **3**, and **5** compounds) are distributed mainly on the A and B-rings, while the LUMO frontier orbitals are allocated to the C-ring. The only exception is observed for the galangin compound. The HOMO molecular orbital of galangin (**4**) is localized mainly on the C2-C3 double bond of C-ring while the LUMO is localized mainly to the B-ring. As stated above to the electronic parameters paragraph, the electron donating capacity of a molecule can be predicted also by the HOMO values; a high HOMO value is in accordance with a strong capacity to donate electrons.[27,28,44] It can be seen from Table 1 that the quercetin (**1**) and galangin (**4**) possesses the highest HOMO values among the five flavonoids, while naringenin (**2**) holds the lowest. Vitexin (**5**) and luteolin (**3**) owns the same ability to donate electron as naringenin (**2**). In case of naringenin (**2**) and vitexin (**5**), the low capacity to donate electrons could be attributed to the lack of C2-C3 double bound (**1**) or the sugar group (**5**). From the HOMO and LUMO energies, ESP and charge distribution maps indicate that the region occupied by the sugar group exerts diminished reactivity. Based on these arguments, the trend for computed HOMO corresponds to the arrangement: quercetin> galangin> uteolin>vitexin>naringenin. The LUMO values indicated that luteolin and galangin are the most electrophilic compounds and possible with the higher anticancer activity. Another parameter with importance is the band gap (ΔE) of these five compounds. A lower ΔE value corresponds to a great antioxidant capacity and a highly reactive system. The band gaps of quercetin and its four analogs range between 3.957 to 4.834 eV. The band gap energy difference between quercetin and luteolin is only 0.08 eV, whereas for naringenin and vitexin it is about 0.87 and 0.20 eV, respectively. This indicates that in any excitation process quercetin and luteolin need less energy than naringenin and vitexin. Interestingly, there is no energy gap difference between quercetin and galangin. This suggests that the two compounds behave in the same way. The analysis of the band gap values for all five flavonoids is consistent with the results of the HOMO and LUMO frontier orbitals. According to AM1 calculation, quercetin and vitexin compounds are expected to be the most stable compounds from the heat of formation values point of view. Galangin has the highest heat of formation, indicating that it is relatively unstable and likely prone to nucleophilic attack compared with quercetin or vitexin. This is supported by the ESP plot for galangin (**4**, Fig. 2), which presents a large area of positive values (blue shade) near to the negative charged 3-OH and 4-carbonyl groups, indicating that this region is prone to nucleophilic attack. The lack of 3',4'-OH groups could also be associated with this relatively instability. The same situation was observed for naringenin. All five electrostatic potential plots (Fig. 2) shows an electronegative potential region (red shade) near to the oxygen atoms of the A-, B- and C-rings meaning that this area is susceptible to electrophilic attack. This suggests that the polar OH group, particularly the carbonyl group in ring C, plays an important role in anticancer activity. Additionally, the potential (μ), electronic hardness (η), electrophilicity index (ω), and global softness (σ) parameters as complementary information for chemical reactivity of molecules were computed. The corresponding values listed in Table 1 are in good agreement with the HOMO and LUMO energies, band gap energies and ESP results. The Fukui indices plot (Fig. 3, Figs. 1S and 2S) provide information about the local reactivity emphasizing the atomic sites available for nucleophilic or/and electrophilic attack. Only the significant values of the Fukui indices which correspond to the highest picks of the Fukui plot (Fig. 3) were analyzed. We note that the HOMO Fukui values for naringenin (**2**), characterized the O2, C8 and C20 atoms as more reactive towards an electrophilic attack while the LUMO Fukui values characterized the O2, C10, C11 and C17 atoms as susceptible to a nucleophilic attack. The C12 and C14 atoms of luteolin (**3**) are preferred places for an electrophilic attack showing the highest HOMO values while the C9, C11, and C17 atoms are preferred places for a nucleophilic attack with highest LUMO values. For galangin (**4**), the highest Fukui HOMO values are assigned to C10 and C13 atoms (0.137 and 0.217 hartrees) suggesting favorable places for electrophilic attacks. The similar Fukui LUMO

values for C8, C9 and O4, C20 atoms of galangin (0.154, 0.160 and 0.109, 0.101 hartrees) reveals that these four atoms are equivalent atomic sites for nucleophilic attack. In case of vitexin (**5**), the significant Fukui HOMO value was observed for C16 atom suggesting a great reactivity of this atom in the electrophilic reactions. The atomic Fukui values also correlate with the result of ESP and charge distribution plots. Taken together, these data highlights that the distribution and number of OH groups, as well as the double bond between C2 and C3 on the flavonoid scaffold are important features for their biological activity.

Lipinski rule of five and ADMET analysis. Output results from Table 2 showed that four out of five compounds fulfilled the Lipinski rule of five. The only exception is vitexin (**5**) as follows: (i) the HBD numbers and TPSA value of vitexin (**5**) are higher compared to HBD and TPSA of the four flavonoids (ii) the XlogP is very low (iii) one rule violation. All these shortcomings can be assigned to the presence of glycosyl group. More specific analysis of pharmacological properties was inspected from ADME results which are listed in Table 3.

The QikProp properties and descriptors presented in Table 3 are considered key parameters for the estimation of absorption and distribution of drugs within the human body. From Table 2 and Table 3, it is revealed that naringenin, luteolin and galangin have lower TPSA and PSA, respectively than quercetin and vitexin suggesting that these compounds have better oral bioavailability. These three compounds are also in acceptable range for QPlogPo/w, QPlogS, and QPlogHERG, except for the naringenin which have a slightly lower value that the accepted one (-4.73 instead of below -5). More interestingly, these three analogues showed higher percent human oral absorbtion (e.g. ranging from 62.05% to 78.58%), Caco-2 cell permeability and brain/blood predicted permeability as compared to quercetin and vitexin values. This analysis revealed that galangin possessed the best pharmacological profile while vitexin the lowest pharmacological profile compared to quercetin. Thus, naringenin, luteolin, and galangin could be potential anticancer agents with enhanced pharmacological properties as compared to quercetin.

Table 1

The calculated electronic features heat of formation, HOMO and LUMO energies, ΔE, chemical potential (μ), electronic hardness (η), electrophilicity index (ω), global softness (σ) for all five flavonoids

ID	ΔH_f^{θ} (kcal/mol)	E_{LUMO} (eV)	E_{HOMO} (eV)	ΔE (eV)	μ (eV)	η (eV)	ω (eV)	σ (eV)
1	-211.719	-2.094	-6.054	3.960	-4.074	3.960	2.096	0.253
2	-147.765	-1.478	-6.312	4.834	-3.895	4.834	1.569	0.207
3	-172.867	-2.173	-6.213	4.040	-4.193	4.040	2.176	0.248
4	-123.555	-2.170	-6.127	3.957	-4.149	3.957	2.175	0.253
5	-366.742	-2.144	-6.303	4.159	-4.224	4.159	2.145	0.240

Table 2

Lipinski rule of five filter including TPSA for five flavonoids

ID	MW	HBA	HBD	XlogP	RotB	TPSA	LRo5 violation
1	302.24	1	5	-1.06	1	131.36	0
2	272.25	1	3	0.24	1	86.99	0
3	286.24	1	4	-0.18	1	111.13	0
4	270.24	1	3	0.49	1	90.9	0
5	432.38	6	7	-2.36	3	181.05	1

Table 3

ADME parameters prediction for five flavonoids using QikProp module

ID	PSA[a]	QPlogPo/w[b]	QPlogS[c]	QPPCaco[d]	QPlogBB[e]	QPlogHERG[f]	%HOA[g]
1	141.943	0.362	-2.830	20.000	-2.352	-5.035	52.34
2	99.508	1.549	-3.146	139.12	-1.311	-4.73	74.38
3	120.34	0.941	-3.039	45.023	-1.91	-5.022	62.05
4	94.58	1.776	-3.251	201.37	-1.198	-5.141	78.58
5	187.17	-0.974	-2.949	3.7340	-3.352	-5.184	18.52

[a] polar surface area < 140Å^2, [b] predicted octanol/water partition coefficient, logP (acceptable range -2 to 6.5), [c]predicted aqueous solubility, logS; S in moldm^{-3} (acceptable range -6.5 to 0.5), [d] predicted apparent Caco-2 cell permeability in nm/sec (acceptable range: <25 poor, >500 great), [e] predicted brain/blood partition coefficient, (acceptable range: -3.0 to 1.2), [f] predicted IC50 value for blockage of HERG K^+ channels, (acceptable range: below -5), [g] predicted human oral absorbtion on 0 to 100% scale, (acceptable range: <25% poor, >80% high).

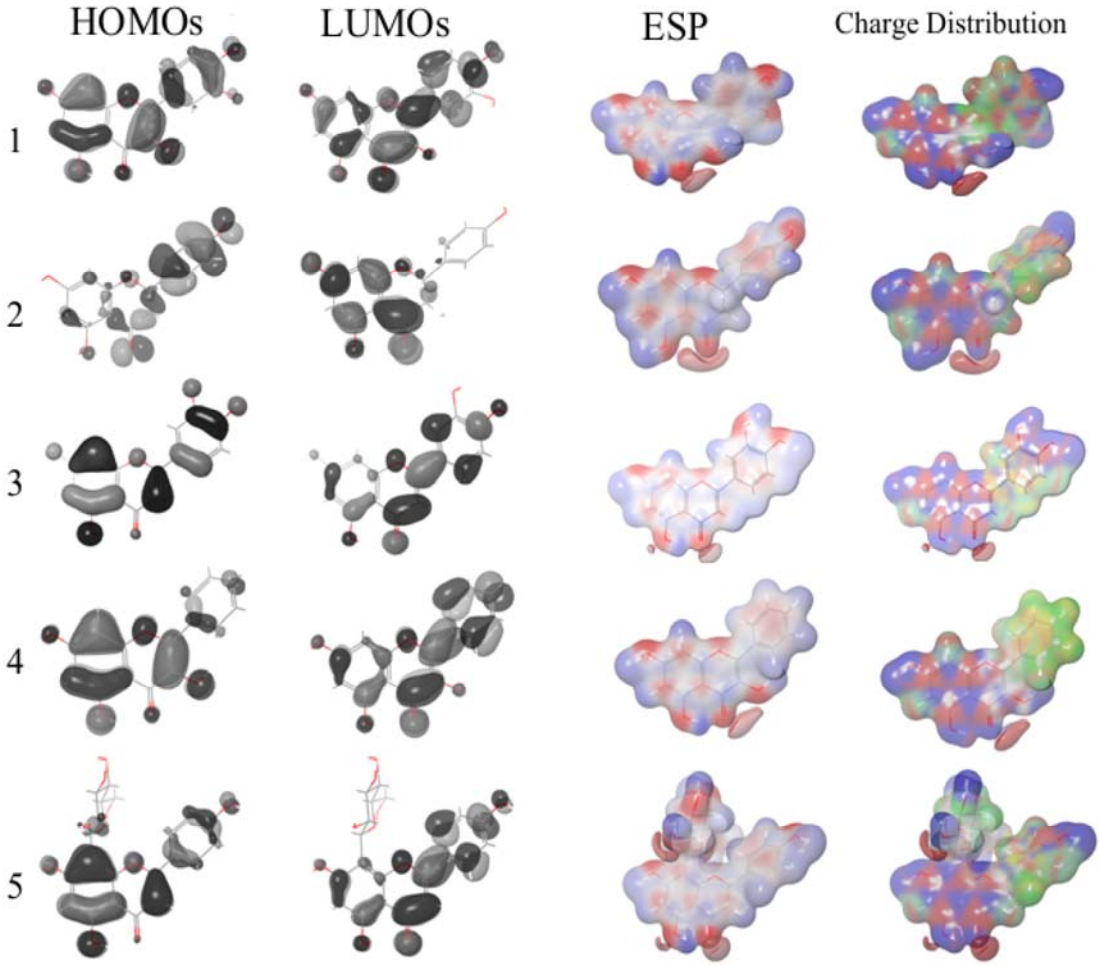


Fig. 2 – Three dimensional HOMOs and LUMOs orbitals,
electrostatic potential profiles and charge distributions of the five flavonoid optimized structures.

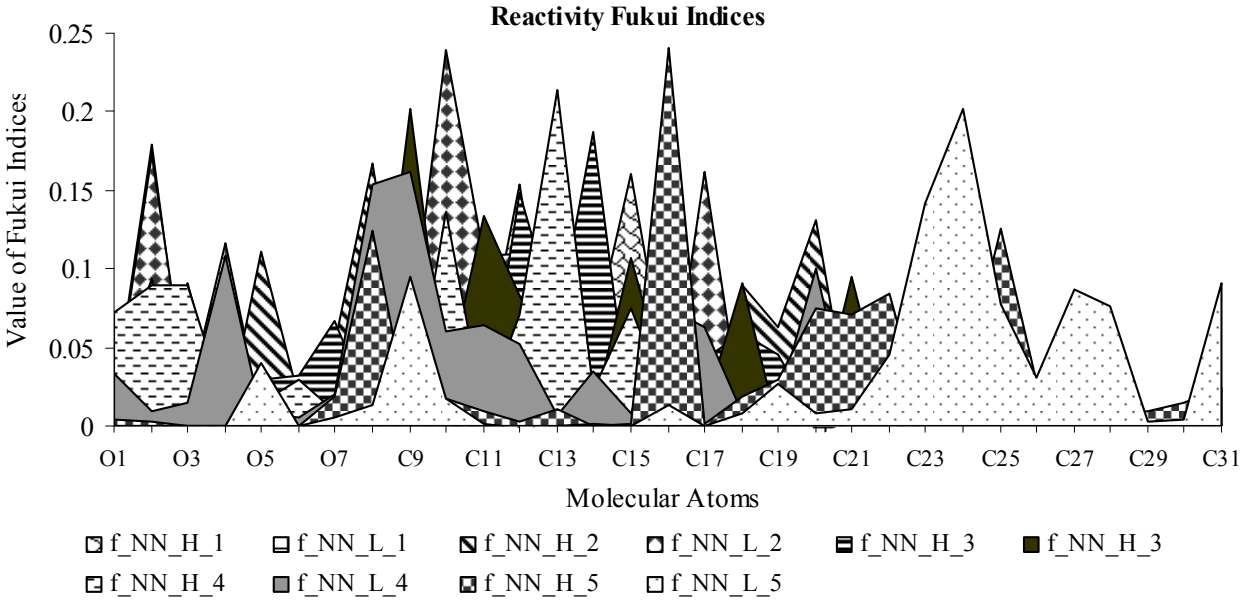


Fig. 3 – Plot of the reactivity Fukui indices of all five flavonoids calculate by DFT-B3LYP/6-31G**-level; (f_NN_H_1Code = fukui_electron density_HOMO_compound 1…5; f_NN_L_1Code = fukui_electron density_LUMO_compound 1….5; the pattern code is associated with the corresponding value of each Fukui atom).

CONCLUSIONS

In the present paper, we have utilized the AM1 and DFT calculations in conjunction with the ADME predictions to explore the structural features and pharmacological profile of five flavonoid compounds. Our study indicates that the distribution and number of OH groups as well as the double bond between C2 and C3 on the flavonoid scaffold are important features for anticancer activity. ADME analysis revealed that naringenin, luteolin, and galangin could be potential anticancer agents with enhanced pharmacological properties as compared to quercetin. Results obtained from the present study will be useful for an efficient design of new flavonoid derivatives as anticancer agents.

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