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A Theoretical Study on the Chemopreventive Activity of Flavonoid Compounds[#]

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Abstract

A structural and electronic characterization of some flavonoid compounds with chemopreventive activity shows that some structural and electronic features of the compounds studied are relevant to understand their biological activity. The flavonoid compounds studied were classified as having an electron–accepting character and the absence of a ring in the structure of the compounds seems to be important to explain the chemopreventive activity presented by these compounds.

Keywords. Flavonoids; chemopreventive activity; DFT.

1 INTRODUCTION

Flavonoids are compounds with diverse chemical structures and are commonly found in fruits, vegetables, nuts and seeds. They are found at relatively high concentrations in the human diet and comprise several classes of molecules including flavonols, flavonones, flavanols and flavans. Flavonoid compounds have received considerable attention in recent years and a variety of properties have been attributed to them on several recent reports such as metal binding capacity, antioxidant activity, ability to affect the endocrine system and ability to prevent the enzymatic activation in carcinogenesis [1].

Some flavonoid compounds are able to protect rodents against chemically–induced carcinogenesis, such as the flavonol and flavan classes and the quercetin molecule [2,3] and many efforts have been made to summarize and elucidate the structure–activity relationship (SAR) of

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these compounds [4–6]. Nowadays, this type of SAR studies has been proven to be helpful in the understanding of the influence of molecular properties on the biological activity presented by several kinds of compounds.

The flavonoid compounds studied in this work were isolated from *Tephrosia toxicaria* (sw) Pers. (*T. toxicaria*) which is a tropical fish–poisoning plant growing in Sri Lanka and South America and is well–know as a source of rotenoids including deguelin, sumatrol and toxicarol. The stems of *T. toxicaria* were chosen as it is known in the literature that their ethyl acetate–soluble extract significantly induces the quinone reductase (QR) enzyme in cultured Hepa 1c1c7 (mouse hepatoma) cells [5]. Recent studies have reported that the induction of the QR enzyme is considered a major mechanism of protection against carcinogenesis [5,6].

Usually, the carcinogenesis process is divided into three phases: initiation (phase I), promotion (phase II) and progression [7]. Compounds which induce or activate enzymes of the phase II, as QR, have ability to prevent cellular damage [4]. Although it is well known that flavonoid compounds are good antioxidants [8,9], some of them have the ability to induce QR, and the requirements for the QR induction are different for those that present antioxidant activity [4].

The main purpose of this work is to study the influence of steric and electronic properties of five flavonoid compounds found in the stems of *T. toxicaria*, and that present chemopreventive activity, in order to collaborate for the elucidation of their mechanism of action of these flavonoids.

2 MATERIALS AND METHODS

2.1 Chemical Data

The flavonoid compounds studied in this work were isolated and characterized from the stems of the *T. toxicaria* [5]. The general structure of a flavonoid compound, as well as the chemical structure of the flavonoid molecules studied in this work are displayed in Figure 1.

The compound **1** is classified as a butenyflavanone and it is named (2S)–5–hydroxy–7–methoxy–8–[(E)–3–oxo–1–butenyl]flavanone; the compound **2** is classified as a rotenoid and its IUPAC nomenclature is 4',5'–dihydro–11,5'–dihydroxy–4'–methoxytephrosin; the compound **3** is classified as a chalcone known as isoliquiritigenin; the compound **4** is named as genistein and it belongs to isoflavone class; the compound **5** is classified as a flavone and it is known as chrysoeriol [5]. These compounds were used in a QR induction assay with the aim to assess their chemopreventive potential (the induction of QR is considered a major mechanism of protection against tumor initiation [5]).

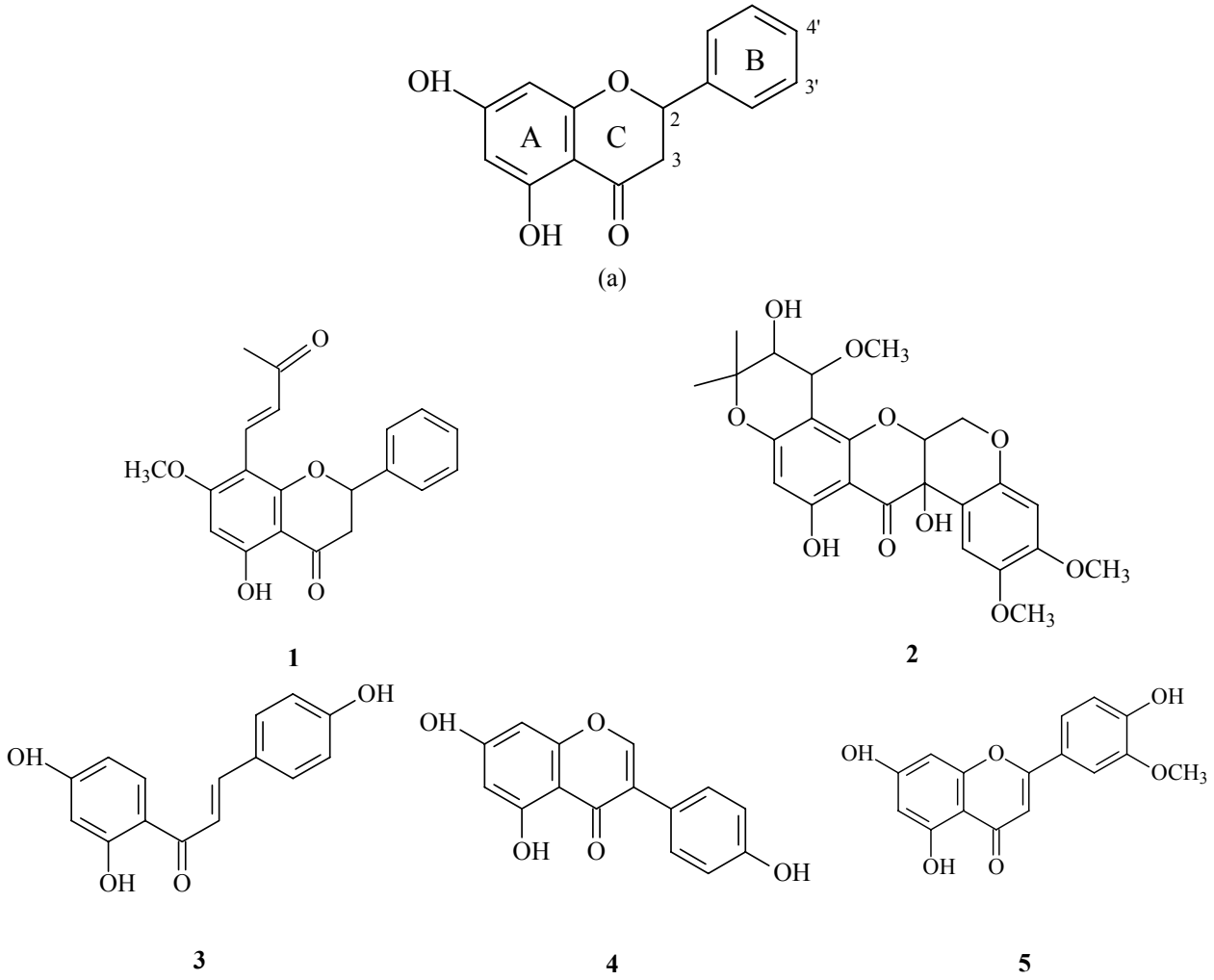

Figure 1. General structure of a flavonoid compound (a), and the chemical structure of the flavonoid molecules studied in this work (numbered as **1**, **2**, **3**, **4** and **5**).

The biological data obtained from the QR induction assay are displayed in Table 1. From Table 1 we can see that compound **3** presents a high chemopreventive activity due to its high CI value (10.1) and compounds **1**, **2**, **4** and **5** present a low chemopreventive activity, *i.e*. they are less active compounds against the QR enzyme, as their CI values are very small when compared to the CI value of compound **3** [5].

Table 1. Biological data obtained for the flavonoid compounds studied by using a quinone reductase (QR) induction assay [5]

Compound	QR [a]		
	CD (μM)	IC_{50} (μM)	CI
1	10.7	14.9	1.4
2	6.7	9.1	1.4
3	3.9	36.3	10.1
4	22.9	45.2	2.0
5	11.7	36.0	3.1

[a] CD = concentration required to double QR activity; IC_{50} = concentration inhibiting cell growth by 50%; CI = chemoprevention index (=IC_{50}/CD). Compounds with CD values <10 μg/mL are considered active.

2.2 Computer Software

2.2.1 Quantum chemistry software

The geometries of the compounds studied in this work were modeled using the molecular mechanics method MM+ [10,11] for a pre–optimization, followed by a conformational analysis performed by the CHEMPLUS program [12]. Afterwards, the Density Functional Theory (DFT) with the B3LYP functional (DFT/B3LYP) [13,14], as implemented in the molecular package GAUSSIAN 98 [15], was used for a final optimization of the compounds studied. The calculations of the molecular properties used to describe the structural and electronic features of the compounds under study were performed by using the DFT/B3LYP and the 6–311G* basis set.

The molecular properties calculated by the DFT method were: total energy (E_T), energy of the highest occupied molecular orbital (E_{HOMO}) and energy of the lowest unoccupied molecular orbital (E_{LUMO}). In addiction, the steric properties surface area (A) and molecular volume (V) were calculated by using the molecular package CHEMPLUS.

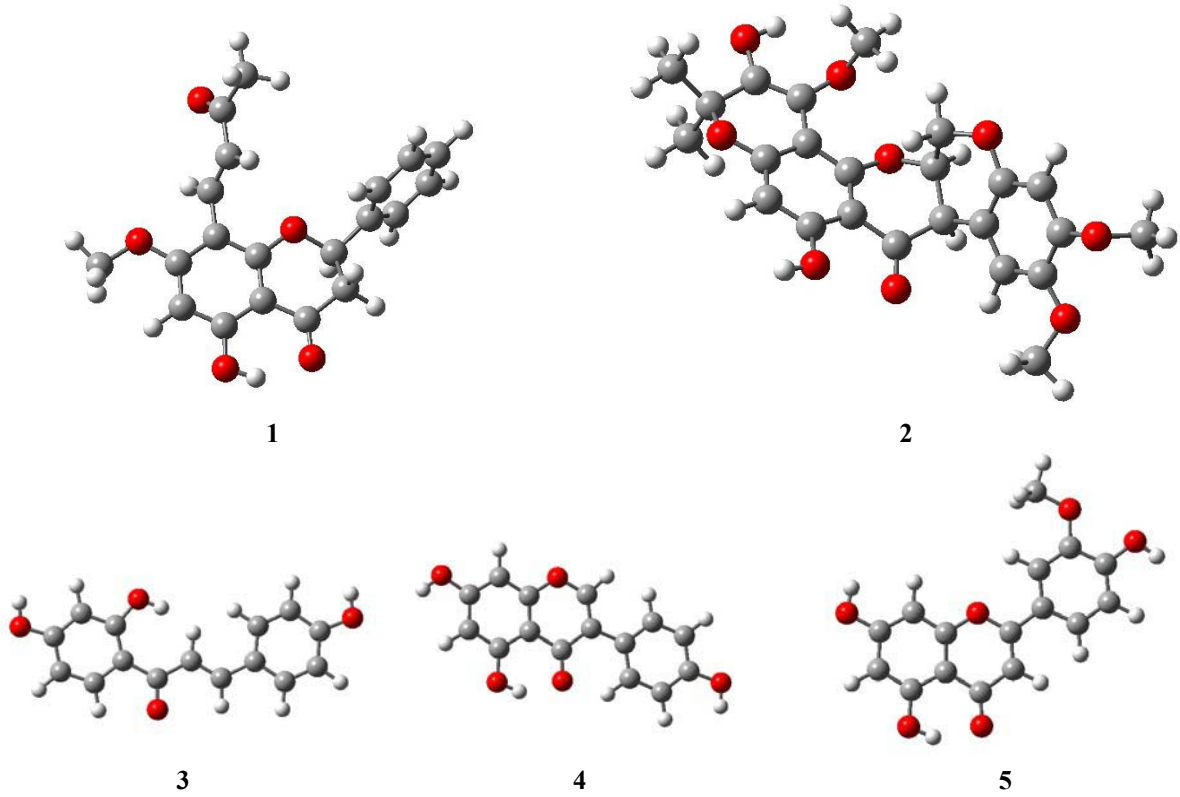

Figure 2. Optimized structure for the flavonoid compounds studied.

3 RESULTS AND DISCUSSION

The optimized structures of each compound studied are displayed in Figure 2; from them we calculated all of the molecular properties used in this work to be correlated with the chemopreventive activity presented by the flavonoid compounds under study.

In Table 2 are shown the obtained values for the steric properties surface area (A) and molecular volume (V). From Table 2 we can notice that compounds **3**, **4** and **5** have similar values for A and V, while compounds **1** and **2** have high values for these steric properties. When we compared the results of Table 2 with the biological data of Table 1, we can see that A and V (that are steric properties related to the whole molecule) are not important properties to explain the chemopreventive activity presented by the flavonoid compounds studied.

Table 2. Molecular properties calculated for the flavonoid compounds studied

	A (Å^2)	V (Å^3)	E_T (a.u.)	E_{HOMO} (a.u.)	E_{LUMO} (a.u.)
1	559.02	954.35	–1149.33	–0.225	–0.067
2	661.08	1163.02	–1606.29	–0.201	–0.056
3	454.61	742.21	–879.88	–0.228	–0.083
4	439.75	720.72	–953.95	–0.212	–0.068
5	486.50	802.01	–1068.50	–0.222	–0.073

Analyzing the calculated total (E_T) energy (displayed in Table 2) for the five flavonoid compounds studied, we can see that the compounds have similar values for these properties and, consequently, the optimized structures have similar chemical stability.

The E_{HOMO} and E_{LUMO} values were calculated because these properties can give an idea on the electron–donating and electron–accepting character of a compound and, consequently, an idea on the probability of a charge transfer complex (CTC) being formed [16]. The energy of the highest occupied molecular orbital (E_{HOMO}) measures the electron–donating character of a compound and the energy of the lowest unoccupied molecular orbital (E_{LUMO}) measures its electron–accepting character [16–21]. From these definitions, two aspects can be observed: (*a*) the greater the E_{HOMO}, the greater the electron–donating capability of the compound and (*b*) the smaller the E_{LUMO}, the smaller the electron–accepting character of the compound [22].

Using the descriptors E_{HOMO} and E_{LUMO}, we were able to classify the flavonoid compounds studied into two classes: electron donor or electron acceptor molecules. Based on the E_{HOMO} and E_{LUMO} values displayed in Table 2, we can see that all flavonoid compounds have similar E_{HOMO} values, while the E_{LUMO} values present relevant differences. Analyzing the E_{LUMO} values obtained

for the compounds studied, we can notice that they have an important characteristic: their low E_{LUMO} values indicate these compounds have an electron–accepting character and, probably, will interact with the biological receptor through a charge transfer mechanism.

In order to have an insight on the main atomic contributions for the LUMO and consequently the possible sites where could occur the entrance of an electron in a charge transfer reaction, we decided to investigate the LUMO plots (which are presented in Figure 3) for the compounds studied.

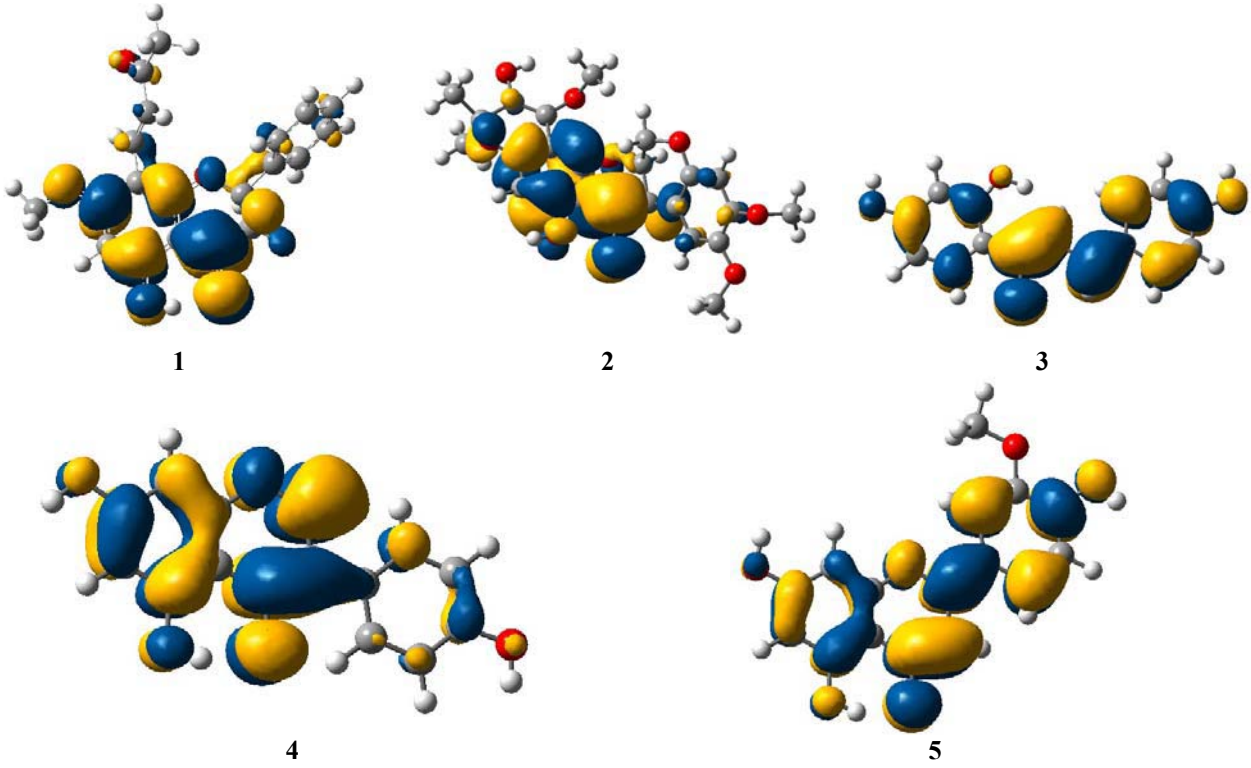

Figure 3. LUMO plots for the flavonoid compounds studied.

From Figure 3 we can see that the atomic contributions for LUMO are similar for the compounds **3** and **5**, *i.e.* the atomic contributions are spread along the whole molecule (A, B and C rings). The exceptions are compounds **1**, **2** and **4**, as the main atomic contributions for LUMO are localized at A and C rings. Comparing the LUMO plots (Figure 3) for the compounds studied, we can see that compounds **3** and **5**, which have the highest activity, present the atomic contributions for LUMO basically from B ring, while compounds **1**, **2** and **4** present no atomic contributions for LUMO from B ring, indicating that the atomic contributions for LUMO from B ring are essential for the chemopreventive activity.

It is also interesting to notice that the most active compound (compound **3**) does not have the C

ring, while the other compounds have it. Therefore, the presence of the C ring in the compound structure probably causes the decrease of its chemopreventive activity. So, we can conclude that structural (absence of the C ring) and electronic (LUMO) aspects can be relevant features to be considered when one is trying to understand the interaction between the flavonoid compounds studied in this work and the QR enzyme.

4 CONCLUSIONS

A theoretical study on the chemopreventive activity of some flavonoid compounds shows that this biological activity has correlation with structural and electronic properties of these compounds.

The calculated E_{LUMO} values showed that the compounds studied can be classified as electron–accepting molecules, indicating that the interaction between the flavonoid compounds studied and the biological receptor can occur through a charge transfer mechanism. Comparing the LUMO plots for the compounds studied, we could see that compounds **3** and **5**, which have the highest activity, present the atomic contributions for LUMO from B ring, while compounds **1**, **2** and **4** present no atomic contributions for LUMO from B ring, indicating that the atomic contributions for LUMO from B ring is essential for the chemopreventive activity.

A comparison between the results obtained in this work and the biological test data for the flavonoid compounds studied shows that structural and electronic aspects can be relevant features to be considered in the understanding of the chemopreventive activity presented by the flavonoid compounds studied in this work.

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