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Theoretical insight into the antioxidant, electronic and anticancer behaviour of s*immondsin*

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Simmondsin is a type of flavonoid it belongs to the group of flavan-3-ols (or simply flavanols (phenols). Phenolic compounds are known as antioxidants. In this study, we explain *simmondsin*'s antioxidant mechanism and investigate it to determine if it can be used as an anticancer therapeutic agent or not. Our results show that *simmondsin* is a very strong antioxidant that prefers hydrogen atom transfer (HAT) mechanism and can be benefited as an anticancer therapeutic agent. Hence, it can be used in cancer drugs to decrease the harmful effects of cancer cure.

Keywords: Anticancer therapeutic agent, Cytochrome P450, Molecular docking, *Simmondsin*

Today, cancer is a very common disease. According to the reports of the International Agency for Research on Cancer (IARC) and the World Health Organization (WHO), the number of cancer patients and cancer-related deaths (deaths from lung, liver, stomach, colorectal, breast, prostate and oesophagel cancer) are expected to increase. Considering these reports, humanity needs new and new chemotherapeutic drugs in the coming years. Therefore, scientists focused on treatments as well as solutions to prevent this disease.[1,2]

In this sense, studies in the fields of health and pharmaceuticals, flavonoids and their antioxidant properties, essential oils and their anticancer therapeutic properties are very important. *Simmondsin* was extracted from defatted jojoba meal according to Elliger *et al.*[3] which has many medical profits such as anti-inflammatory effect[4], wound healing, benefits for skin diseases[5], the antioxidant effect[6], lubricant properties[7]. *Simmondsin*, a part of the chemical family of flavonoids and the main molecule in Jojoba, is known with antifungal, antifeedants and insecticidal effects[8]. However, the effect of *simmondsin* as a pure molecule has not been described yet. Also, in one of our previous studies, we investigated the electronic and thermodynamic properties of a compound formed by methyl alcohol and *simmondsin*[9].

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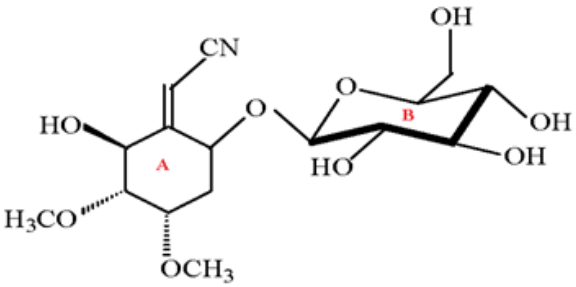
In the literature, there are a few studies dealing with *simmondsin* antioxidant properties through experimental methods. However, we have not encountered yet a study demonstrating the radical scavenging mechanism, anticancer properties, and antioxidant properties of *simmondsin* using theoretical methods.

New therapeutic approaches for cancer treatments aim to produce new anticancer drugs with low toxicity and resistance[10,11]. Therefore, the potential of essential oils (EO) and their components are relatively new in the cancer research area. It affects cell-specific and individualized cancer treatment and cellular mechanisms[12]. EOs prevent the growth of cancer cells and are effective in reducing tumours in animal models[13]. For these, significant effects some of EOs are used in molecular docking calculations with *simmondsin* to compare with the similar effects of *simmondsin* in this paper.

In this article, antioxidant, electronic, and anticancer behaviours of *simmondsin* were investigated from a theoretical perspective. The theoretical studies are more economical and less time-consuming than experimental studies.

Computational methods

First of all, quantum chemical calculations were done for the antioxidant property. The molecular structure of *simmondsin*, descriptors of the antioxidant property calculations in the gas phase, and water, natural bond analysis were examined using density functional theory



Scheme 1 — The molecular structure of *simmondsin*

(DFT) using the B3LYP method with 6-31G (d, p) basis set. These calculations were performed with Gaussian 16[14]. The package program Gauss View 6.0.16[15] was used for the visualization of the structure (Scheme 1).

Antioxidant Property

The mechanisms of flavonoids explaining biological activities are largely unknown[16-20]. The antioxidant effect appears as a result of different phenomena. These may be scavenging of free radicals, sequestration of oxidants, changing the statement of plural genes encoding enzymes with antioxidant function, and changing cell signalling[22].

For the antioxidant property of the compounds, free radicals play a significant role[23]. The antioxidant properties of the flavonoids (F-OH (F represents flavonoid)) are related to the feat of importing phenolic H atoms to free radicals. The antioxidant reactions are described[24-27] as follows:

1. Hydrogen Atom Transfer (HAT).
2. Single Electron Transfer followed by Proton Transfer (SET-PT).
3. Sequential Proton Loss Electron Transfer (SPLET).

In the first reaction, the hydrogen atom is replaced with the free radical:

$$F - OH \rightarrow F - O^{\bullet} + H^{\bullet} \ldots \quad (1)$$

HAT reactions can be characterized by the bond dissociation enthalpy (BDE) of OH group. BDE can be calculated by the following equation:

$$BDE = H(F - O^{\bullet}) + H(H) - H(F - OH) \ldots \quad (2)$$

$H(F - O^{\bullet})$ is the enthalpy of the flavonoid radical; H(H) is the enthalpy of the hydrogen atom; and H(F–OH) is the enthalpy of the main flavonoid molecule. A lower BDE value identifies the better antioxidant property which is attributed to the ability to give a hydrogen atom from the hydroxyl group and results in a simple free radical scavenging reaction.

The second reaction has two steps and the first step in which the replacement occurs is described as follows:

$$F - OH \rightarrow F - OH^{\bullet +} + e^{-} \ldots \quad (3)$$

Adiabatic ionisation potential (AIP) can be calculated as follows:

$$AIP = H(F - OH^{\bullet +}) + H(e^{-}) - H(F - OH) \ldots \quad (4)$$

$H(Fl - OH^{\bullet +})$ is the enthalpy of the radical cation and $H(e^{-})$ is the enthalpy of the electron. The second step is described as follows:

$$F - OH^{\bullet +} \rightarrow F - O^{\bullet} + H^{+} \ldots \quad (5)$$

PDE is described below:

$$PDE = H(F - O^{\bullet}) + H(H^{+}) - H(F - OH^{\bullet +}) \ldots \quad (6)$$

$H(H^{+})$ is the enthalpy of the proton.

The proton affinity (PA) can be calculated by following equation[28,29]:

$$PA = H(F - O^{-}) + H(H^{+}) - H(F - OH) \ldots \quad (7)$$

$H(F - O-)$ is the enthalpy of the flavonoid anion. In the second step, electron transfer may occurring the following way:

$$F - O^{-} \rightarrow F - O^{\bullet} + e^{-} \ldots \quad (8)$$

The equation which is related to electron transfer enthalpy (ETE) is given in equation 9.

$$ETE = H(F - O^{\bullet}) + H(e^{-}) - H(F - O^{-}) \ldots \quad (9)$$

SET-PT and SPLET mechanisms are preferred for radicals with high electron affinity.

Molecular Docking

For the molecular docking calculations[30], the crystal data for the protein structure of cytochrome P450 (PDB ID:1PQ2) were obtained from Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank. Water molecules and pre-existing ligands were omitted and Kollman partial charges were added by using Auto Dock Tools[31]. Molecular docking calculations and analysis of ligand-enzyme interactions were performed by using iGEMDOCK[32]on the basis of GEMDOCK[33], and the visualization of the docking positions were maintained by PyMol package[34].

Results and Discussion

Before the antioxidant activity and molecular docking process, the stable structures of the *simmondsin* in gas and in water were determined. The stable structure of the *simmondsin* in gas was given in (Fig. 1).

Antioxidant and Electronic Properties

The most essential things for the antioxidant property of a molecule are the energy and the

distribution of the frontier orbitals which are also given information about the electronic properties of molecules. The energy of LUMO (Lowest Unoccupied Molecular Orbital) presents the ability to acquire electrons while the energy of HOMO (Highest Occupied Molecular Orbital) presents the ability to donate electrons. As seen from the (Fig. 2), the HOMO orbitals are distributed over the OH groups in the molecule. This means that the HOMO orbitals region could be easily assaulted by free radicals. Also, the higher HOMO orbital energy is the presentation of the stronger electron-donating abilities, as a result, *simmondsin* in the gas phase has stronger electron donating ability than *simmondsin* in water as seen in (Table 1).

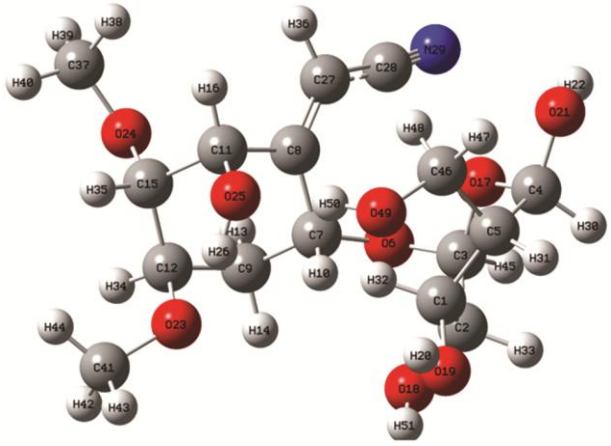


Fig. 1 — Optimized geometry of *simmondsin* in gas

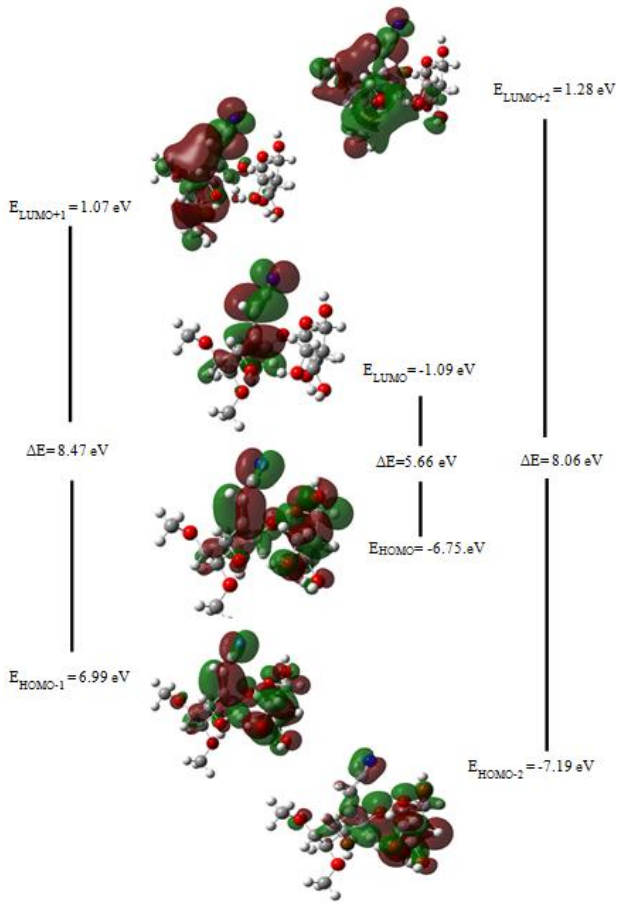


Fig. 2 — Molecular orbitals compositions of *simmondsin*

To determine the antioxidant property of a molecule, it is required to analyse electronegativity, electron affinity, hardness, and electrophilicity index. The values represented in (Table 1) point out that *simmondsin* acts as the electron donor and also that is an indication of the antioxidant activity of *simmondsin*[35].

Inorganic compounds, electronic transitions are usually as π (donor) →π* (acceptor) and n → π* transitions[35]. Time- dependent density functional theory (TD-DFT) calculations[36] in the gas phase and also in water environment were performed on *simmondsin* employing B3LYP/6-31G (d, p) functional in order to comprehend the electronic transitions of a molecule. (Table 2), shows the electronic transitions, major contributions, calculated absorption peaks (kmax's), excitation energies, oscillator strengths (f) and assignments of the transitions of the *simmondsin*.

The electronic absorption peak (at 248 nm in gas and 251 nm in water) corresponds to transition from the ground state to the first excited state, which corresponds to HOMO to LUMO excitation in both the phases with high oscillator strengths. This band arises from an n → π* transition. The second absorption band at 236 nm arises from HOMO-2 to LUMO transition in the gas phase and at 249 nm arise from HOMO-1 to LUMO in the water environment. However, the oscillator strength for the second transition is lower than the first transition. The third absorption at 228 nm (in gas) and 247 nm (in water) arise from HOMO-4 to LUMO

Table 1 — Molecular descriptors of *simmondsin* calculated at B3LYP/6-31 g (d, p) level

Parameters	Gas	Water
E_{LUMO} (eV)	–1.09	–1.31
E_{HOMO} (eV)	–6.75	–6.92
ΔE= E_{LUMO}- E_{HOMO} (eV)	5.67	5.61
I (ionization potential) (eV)	6.75	6.92
A (electron affinity) (eV)	1.09	1.31
χ (electronegativity) (eV)	3.92	4.12
η (global hardness) (eV)	2.83	2.81
S (global softness) (eV^{-1})	0.35	0.36
μ (electronic chemical potential) (eV)	–3.92	–4.12
ω (global electrophilicity index) (eV)	2.71	3.02

Table 2 — Calculated absorption wavelengths, energies and oscillator strengths of *simmondsin* using the TD-DFT method at the B3LYP/6- 31G (d,p) level

Excitation Major Contribution*	CI expansion coefficient	Wavelength Calc. Gasphase (nm)	Excitation Energy (eV)	Oscillator Strength (f)	Excitation	CI expansion coefficient	Wavelength Calc. Water (nm)	Excitation Energy (eV)	Oscillator Strength (f)
Excited State 1	Singlet-A				Excited State 1	Singlet-A			
95 →101 (3%) (HOMO-5→ LUMO)	0.11798	247.99	4.99	0.0102	97 →101 (8%) HOMO-3→ LUMO	0.19754	251.24	4.94	0.0260
98 →101 (7%) (HOMO-2 →LUMO)	-0.18751				98 →101 (5%) HOMO-2→ LUMO	0.15658			
99 →101 (19%) (HOMO-1→LUMO)	-0.31215				100 →101 (84%) HOMO → LUMO	0.64877			
100 →101 (68%) (HOMO→ LUMO)	0.58494								
Excited State 2					Excited State 2				
94 →101(7%) (HOMO-6→ LUMO)	-0.18068	236.02	5.25	0.0096	98 →101 (20%) HOMO-2→ LUMO	-0.31511	249.07	4.98	0.0131
95 →101(10%) (HOMO-5→ LUMO)	-0.21878				99 →101 (76%) HOMO-1→ LUMO	0.61602			
97 →101 (8%) HOMO-3→ LUMO	0.19705				100 →101 (2%) HOMO → LUMO	0.10613			
98 →101 (57%) HOMO-2→ LUMO	0.53200								
99 →101 (2%) HOMO-1→ LUMO	0.10441								
100 →101 (13%) HOMO → LUMO	0.25722								
Excited State 3					Excited State 3				
96 →101 (55%) HOMO-4→ LUMO	0.52420	228.84	5.42	0.0506	93 →101 (3%) HOMO-7→ LUMO	-0.19196	247.99	5.24	0.0102
98 →101 (7%) HOMO-2→ LUMO	0.18738				94 →101 (13%) HOMO-6→ LUMO	-0.25480			
99 →101 (32%) HOMO-1→ LUMO	-0.39918				95 →101 (8%) HOMO-5→ LUMO	-0.20364			
100 →101 (3%) HOMO → LUMO	-0.12425				96 →101 (40%) HOMO-4→ LUMO	0.44963			
					97 →101 (22%) HOMO-3→ LUMO	0.33534			
					100 →101 (4%) HOMO → LUMO	-0.13540			

*The major contribution rate of HOMO–LUMO orbitals are determined by using the Gauss Sum 2.2 program[37]

excitation. Also, the oscillator strength for the second transition is lower than the third transition (Fig. 2).

To determine the antioxidant property of a molecule, it is required to analyse electronegativity, electron affinity, hardness, and electrophilicity index. The values represented in (Table 1) point out that *simmondsin* acts as the electron donor and also that is an indication of the antioxidant activity of *simmondsin*[38].

Bond dissociation enthalpy (BDE) is a numerical parameter associated with the HAT mechanism which identifies the stability of the O-H bond. BDE value of the related O-H bond is low, the bond can be split up easily and the lower BDE value indicates the higher antioxidant capacity of the molecule[39].

According to (Table 3), calculated BDE values in the gas phase and in water indicate that hydrogen atom abstraction from O19 has the highest antioxidant activity while the hydrogen atom abstraction from O18 is the lowest antioxidant capacity. Besides, *simmondsin* shows better antioxidant capacity in the gas phase than in water and the B-ring of *simmondsin* plays an important role in the HAT mechanism.

For the SET-PT mechanism, adiabatic ionization potential (AIP) and proton dissociation enthalpy (PDE) are important parameters. AIP defines electron forgiving by the antioxidant molecule. *Simmondsin* in water has a low AIP parameter than in the gas phase, so *simmondsin* in water exhibits strong antioxidant property. The low value of the PDE parameter indicates that the SET-PT mechanism is energetically preferred for the antioxidant activity[40]. For the calculated values of PDE, hydrogen atom abstraction from O19 the atom has much more antioxidant activity than the hydrogen atom abstraction from O18, and AIP and PDE values in water are significantly lower than that in the gas phase. In the gas phase, *simmondsin* didn't prefer the SET-PT mechanism for the antioxidant activity because of the huge AIP values. However, the SET-PT mechanism can be preferred for the water environment.

SPLET mechanism is one of the important antioxidant mechanisms in which antioxidants catch free radicals and also the radical scavenging activity of a molecule can be analysed with this mechanism. For the SPLET mechanism the PA and ETE parameters are very significant. PA values of *simmondsin* are higher in gas compared to the values in water while the ETE parameters are lower in gas than in water. Therefore, SPLET mechanism is favoured for the water environment.

Natural bondorbital (NBO) analysis

The NBO method is an efficient method to expose the intra- and inter-molecular bonding and interaction between bonds, and the electron delocalisation from the lone pairs' atoms. We have calculated the second- order Fock matrix of a compound formed by *simmondsin* and methyl alcohol comparing the two different conformations, previously. In this paper, I especially focused on the lone pairs of the oxygen atoms of *simmondsin*. The NBO analysis of oxygen and one nitrogen atoms to the neighboring antibonding σ*and π* orbitals (Table 4). Evaluation of the delocalisation or hyperconjugation of the various second-order inter actions between the occupied orbitals of the atom and empty orbitals of another atom DFT calculation is used[35]. The equation below is used for the hyperconjugative interaction energy E(2) revealed from the second-order perturbation approximation.

$$E(2) = -n_\sigma \frac{\langle \sigma | F | \sigma \rangle^2}{\varepsilon_{\sigma^*} - \varepsilon_\sigma} = -n_\sigma \frac{F_{ij}^2}{\Delta E} \quad \cdots \quad (3.1)$$

In the equation; $\langle \sigma | F | \sigma \rangle^2$ or F_{ij}^2 represents the Fock matrix element between i and j NBO orbitals, ε_σ and ε_{σ^*} are the energies of σ and σ* orbital's, and n_σ is the population of the donor σ orbitals[35].

NBO analysis has been applied to the *simmondsin* at the DFT/B3LYP/6- 31G (d, p) level so as to clarify, the intra-molecular rehybridization and delocalisation of electron density within the molecule. The second-order perturbation theory analysis of the Fock matrix in the NBO basis of *simmondsin*, presents strong intra-molecular hyper-conjugative interactions, and is presented in (Table 4). As seen from the (Table 4), hyperconjugative interactions between π (C_8 - C_{27}) bonding orbital and π^* (C_{28} - N_{29}) anti- bonding orbital obviously indicate the forceful delocalisation. The very strong interaction between the lone pair n2 (O6) with that of antibonding C3 – O17, the lone pair n2 (O21) with that of antibonding C4 – O17 and the lone pair n1 (N29) with that of antibonding C27 – C28 with stabilization energy 13.24, 11.71 and 12.17 kcal/mol respectively, remark larger delocalisation. Another significant addition for the molecular stabilization for the intra-molecular interaction created by the orbital overlap between the lone pair n2 (O_{23}) and σ* (O25 – H26) antibonding orbitals with stabilization energy 9.68 kcal/mol, which concluding in the formation of intra-molecular O - H...O bonds.

Molecular Docking

The applications of EOs as anticancer therapeutic agents and the process for the discovery of anticancer

Table 3 — Antioxidantparameters of *simmondsin* in the gas and water environment

Bond	BDE (Hartree)		AIP (Hartree)		PDE (Hartree)		PA (Hartree)		ETE (Hartree)	
	gas	water	gas	water	gas	water	gas	water	gas	water
O18-H	0.161856	0.657201	0.29349	0.226186	0.368638	0.017375	0.534235	0.096273	0.127893	0.147288
O19-H	0.15003	0.648265	0.29349	0.226186	0.356812	0.008439	0.556751	0.081554	0.093551	0.153071
O21-H	0.161442	0.652448	0.29349	0.226186	0.368224	0.012622	0.569361	0.077459	0.092353	0.161349
O25-H	0.15549	0.650246	0.29349	0.226186	0.362272	0.01042	0.548865	0.092116	0.106897	0.14449
O49-H	0.153063	0.651322	0.29349	0.226186	0.359845	0.011496	0.55675	0.07082	0.096585	0.166862

Table 4 — The selected values of second-order perturbation energies E(2) (kcal/mol) corresponding to the most important charge transfer interaction (donor–acceptor) in *simmondsin* by DFT/B3LYP/6-31G (d, p) method (*Contd*.)

Lonepair	Occupancy	Donor-acceptorinteraction	Hybrid (% p character)	E(2)[a] (kcal/mol)	E(j)-E(i)[b] (a.u.)	F(i,j)[c] (a.u.)
$LP_1\ O_6$	1.95997	n ($LP_1\ O_6$) →σ*(C_2 - C_3)	$Sp^{1.52}$ (60.35)	3.19	0.87	0.047
		n ($LP_1\ O_6$) →σ*(C_7 - H_{10})		3.03	1.01	0.049
$LP_2\ O_6$	1.89141	n ($LP_2\ O_6$) →σ*(C_2 - C_3)	$Sp^{99.99}$ (99.84)	5.67	0.63	0.054
		n ($LP_2\ O_6$) →σ*(C_3 – O_{17})		13.24	0.59	0.080
		n ($LP_2\ O_6$) →σ*(C_7 – C_8)		8.81	0.70	0.071
$LP_1\ O_{17}$	1.94587	n ($LP_1\ O_{17}$) →σ*(C_2 - C_3)	$Sp^{1.33}$ (56.98)	2.87	0.90	0.045
		n ($LP_1\ O_{17}$) →σ*(C_3 – O_6)		2.94	0.88	0.046
		n ($LP_1\ O_{17}$) →σ*(C_4 – O_{21})		4.01	0.88	0.053
$LP_2\ O_{17}$	1.91953	n ($LP_2\ O_{17}$) →σ*(C_2 - C_3)	$Sp^{99.99}$ (99.48)	2.49	0.64	0.036
		n ($LP_2\ O_{17}$) →σ*(C_3 – O_6)		2.69	0.62	0.037
		n ($LP_2\ O_{17}$) →σ*(C_3 – H_{45})		6.78	0.77	0.065
		n ($LP_2\ O_{17}$) →σ*(C_4 – C_5)		5.79	0.68	0.057
		n ($LP_2\ O_{17}$) →σ*(C_4 – H_{30})		4.68	0.74	0.053
$LP_1\ O_{18}$	1.97757	n ($LP_1\ O_{18}$) →σ*(C_1 – C_2)	$Sp^{1.06}$ (51.54)	2.43	0.97	0.044
$LP_2\ O_{18}$	1.95136	n ($LP_2\ O_{18}$) →σ*(C_1 – C_2)	$Sp^{99.99}$ (99.70)	3.97	0.67	0.046
		n ($LP_2\ O_{18}$) →σ*(C_2 – H_{33})		7.87	0.73	0.068
$LP_1\ O_{19}$	1.97749	n ($LP_1\ O_{19}$) →σ*(C_1 – H_{32})	$Sp^{1.27}$ (56.01)	2.69	1.04	0.048
$LP_2\ O_{19}$	1.95532	n ($LP_2\ O_{19}$) →σ*(C_1 – C_5)	$Sp^{20.09}$ (95.19)	7.99	0.70	0.067
		n ($LP_2\ O_{19}$) →σ*(C_1 – H_{32})		2.33	0.80	0.039
$LP_1\ O_{21}$	1.97548	n ($LP_1\ O_{21}$) →σ*(C_4 – C_5)	$Sp^{1.18}$ (54.18)	1.24	0.96	0.031
		n ($LP_1\ O_{21}$) →σ*(C_4 – H_{30})		1.94	1.02	0.040
$LP_2\ O_{21}$	1.93337	n ($LP_2\ O_{21}$) →σ*(C_4 – H_{30})	$Sp^{66.66}$ (98.43)	5.95	0.75	0.060
		n ($LP_2\ O_{21}$) →σ*(C_4 – O_{17})		11.71	0.60	0.075
$LP_1\ O_{23}$	1.95903	n ($LP_1\ O_{23}$) →σ*(O_{25} – H_{26})	$Sp^{1.61}$ (61.68)	2.90	1.01	0.048
		n ($LP_1\ O_{23}$) →σ*(C_{41} – H_{44})		3.28	0.98	0.051
$LP_2\ O_{23}$	1.91571	n ($LP_2\ O_{23}$) →σ*(C_{12} – C_{15})	$Sp^{18.78}$ (94.90)	5.02	0.70	0.053
		n ($LP_2\ O_{23}$) →σ*(O_{25} – H_{26})		9.68	0.81	0.080
		n ($LP_2\ O_{23}$) →σ*(C_{41} – H_{42})		6.35	0.78	0.064
$LP_1\ O_{24}$	1.96382	n ($LP_1\ O_{24}$) →σ*(C_{12} – H_{35})	$Sp^{1.35}$ (57.44)	2.76	0.99	0.047
$LP_2\ O_{24}$	1.91810	n ($LP_2\ O_{24}$) →σ*(C_{11} – C_{15})	$Sp^{99.99}$(99.87)	9.15	0.63	0.068
		n ($LP_2\ O_{24}$) →σ*(C_{15} – H_{35})		3.37	0.73	0.045
		n ($LP_2\ O_{24}$) →σ*(C_{37} – H_{38})		6.54	0.73	0.063
		n ($LP_2\ O_{24}$) →σ*(C_{37} – H_{40})		5.27	0.73	0.056
$LP_1\ O_{25}$	1.96762	n ($LP_1\ O_{25}$) →σ*(O_{49}– H_{50})	$Sp^{1.32}$ (56.87)	3.37	1.06	0.054
$LP_2\ O_{25}$	1.94290	n ($LP_2\ O_{25}$) →σ*(C_{11} – C_{15})	$Sp^{37.80}$ (97.35)	3.57	0.65	0.043
		n ($LP_2\ O_{25}$) →σ*(C_8 – C_{11})		6.18	0.72	0.060
		n ($LP_2\ O_{25}$) →σ*(O_{49}– H_{50})		2.53	0.81	0.041

(*Contd*.)

Table 4 — The selected values of second-order perturbation energies E(2) (kcal/mol) corresponding to the most important charge transfer interaction (donor–acceptor) in *simmondsin* by DFT/B3LYP/6-31G (d, p) method

Lonepair	Occupancy	Donor-acceptorinteraction	Hybrid (% p character)	E(2)[a] (kcal/mol)	E(j)-E(i)[b] (a.u.)	F(i,j)[c] (a.u.)
$LP_1 N_{29}$	1.96982	n ($LP_1 N_{29}$) →σ*(C_{27} – C_{28})	$Sp^{0.85}$ (46.00)	12.17	1.02	0.100
$LP_1 O_{49}$	1.98289	n ($LP_1 O_{49}$) →σ*(C_{46}– H_{48})	$Sp^{1.14}$ (53.14)	2.47	1.04	0.045
$LP_2 O_{49}$	1.94673	n ($LP_2 O_{49}$) →σ*(C_5– H_{46})	$Sp^{99.99}$ (99.42)	7.39	0.66	0.063
		n ($LP_2 O_{49}$) →σ*(C_{46}– H_{47})		2.97	0.77	0.043
σ (C_{27} – H_{36})	1.96099	σ (C_{27} – H_{36}) →σ*(C_7– C_8)	$Sp^{2.46}$ (71.09)	7.27	0.94	0.074
π (C_{28} - N_{29})	1.98696	π (C_{28} - N_{29}) →π* (C_8 - C_{27})	$Sp^{99.99}$ (99.82)	9.46	0.36	0.053
π(C_8 - C_{27})	1.89028	π (C_8 - C_{27}) →π* (C_{28} - N_{29})	$Sp^{1.00}$ (99.92)	18.16	0.40	0.077
π^* (C_8 - C_{27})	0.10225	π^* (C_8 - C_{27}) →π* (C_{28} - N_{29})	$Sp^{1.00}$ (99.92)	10.03	0.08	0.083

[a]E(2) means energy of hyperconjugative interactions, cf. Eq. (2)
[b]Energy difference between donor and acceptor i and j NBO orbitals
[c]F(i,j) is the Fock matrix element between i and j NBO orbitals

drugs are explained in the previous sections. Therefore, molecular docking behaviours of *simmondsin* along with EOs anticancer agents (colchicine, ellipticine, paclitaxel, vinblastine, and vincristine have been reported to improve the quality of life of the cancer patients by reducing the range of their pain[41] were determined together with Cytochrome P450. In the literature, cytochrome P450 enzymes are known as responsible for the reactions usually contain either inserting or revealing a hydroxyl group, or some other hydrophilic group such as an amine or sulphydryl group, and usually contain hydrolysis, oxidation or reduction mechanisms. At the end of the reactions, little chemical differences make a compound more hydrophilic, so it can be effectively excreted by the excretory system. Briefly, cytochrome P450 enzymes change many drugs, into less toxic forms that are easier for the body to excrete. For these reasons, cytochrome P450 was used as a target macromolecule which plays an active role in the cancer drugs. The results are presented in (Table 5) and proper docking positions are shown in (Fig. 3).

The docking energy value of *simmondsin* is similar to colchicine when the molecular weight is taken into account. *Simmondsin's* van der Waals interaction values are similar to colchicine, ellipticine, vincristine while the hydrogen bond is tighter than vincristine and ellipticine. Hydrogen bonding energies of *simmondsin* with the H-M-GLY amino acid is high while the H-M-LEU, H-S-THR, H-M-THR, and H-S-CYS amino acids are at low level. The strong van der Waals interactions (>2 kcal/mol) exist between *simmondsin* and V-S-LEU, V-M-ALA, V-M-GLY, V-M-THR, V-M-TSR, V-S-PHE residues. As seen from (Fig. 3) ellipticine, colchicine and vincristine are bound to Cytchrome P450 approximately in the same region as *simmondsin*.

Table 5 — The results of molecular docking analysis (Interaction energies in kcal/mol and molecular weights of ligands are in g/mol, VDW: Van der Waals)

Compound	Total Energy	VDW	H-bond	Molecular Weight
Simmondsin	–123.01	–92.98	–30.03	375.374
Colchicine	–121.33	–99.02	–22.32	399.443
Ellipticine	–103.06	–93.37	–9.69	246.313
Paclitaxel	–196.10	–161.99	–34.12	853.918
Vinblastine	–145.46	–133.40	–12.06	811.997
Vincristine	–131.56	–98.27	–33.29	826.988

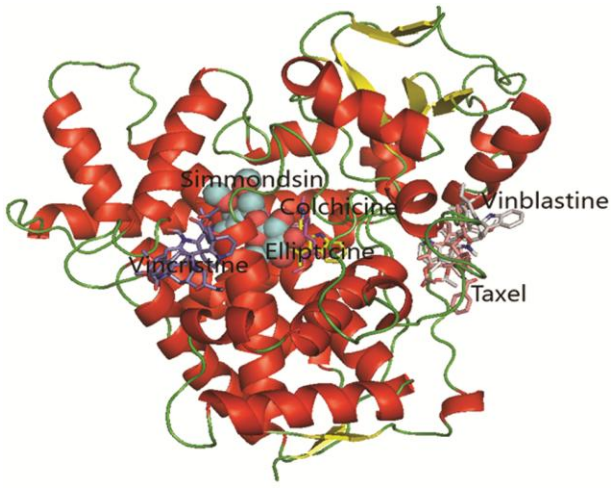


Fig. 3 — Best docked poses for *simmondsin*, colchicine, ellipticine, paclitaxel, vinblastine, vincristine by iGEMDOCK

As the other anticancer agents, s*immondsin* induce apoptosis tumor cell lines and functions as cancer therapy decreasing the effects of the drugs[9].

Conclusion

In this study, the antioxidant properties of *simmondsin* in gas and water environment and its

molecular docking behaviour have been determined. The antioxidant properties of *simmondsin* have been defined theoretically for the first time. This study demonstrated that *simmondsin* has great antioxidant activity when the hydrogen atom abstraction from the O19 atom is in both gas and water environment. For the best antioxidant property, the HAT mechanism has been preferred by *simmondsin* in the gas phase. Also, SET-PT mechanism has been preferred by *simmondsin* in the water environment for the best antioxidant property. Although there are important electronic transitions like π (donor) $\rightarrow\pi^*$ (acceptor) and $n \rightarrow \pi^*$ in the *simmondsin* molecule, it is a stable molecule since the ΔE value between HOMO-LUMO orbitals is large. Furthermore, *simmondsin* is an anticancer therapeutic agent, it has been used to increase the quality of life of the cancer patients as the other EOs and new drug design study.

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Conflict of interest

All authors declare no conflict of interest.

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