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Article

DFT Calculations, Pro-Apoptotic Effects, Anti-Infective Investigations of Alkaloids Isolated from the Stem Bark Extract of *Enantia chlorantha*

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Abstract: Fractionation of the stem bark of *Enantia chlorantha* Oliv yields three alkaloids Palmatine (**1**), Jatrorrhizine (**2**), Columbamine (**3**), and *β*-Sitosterol (**4**). In this investigation, density functional theory (DFT) calculations were carried out to evaluate the electronic structure and properties of **1**-**4** by DFT-B3LYP/6-31G level of theory using Gaussian 09 software. Quantum molecular descriptors of the title compounds: ionization potential (IP) and Electron Affinities (EA), Hardness (η), Softness (S), Electronegativity (μ), Electrophilic Index (ω), Electron Donating Power (ω-), Electron Accepting Power (ω+) and Energy Gap (Eg) have been calculated. The *in vitro* cytotoxicity of the compounds was investigated against MCF-7, HCT116 cancer cell lines using Wi-38 cells as control. The compounds inhibited the proliferation of the MCF-7 and HCT116 cell lines and induced apoptosis *via* up-regulation of caspase-3, Bax, PARP cleavage, and downregulation of Bcl-2. DFT analyses revealed that compounds **1** and **3** have smaller energy gaps, 0.072 and 0.071eV, respectively, with the highest dipole moments, hence, more chemically reactive and exhibited better modulation of caspase-3 enzyme and inhibitory activities of the MCF-3 and HCT116 cell lines. The antimicrobial and antiparasitic evaluation of **1** - **4** showed moderate efficacy against the bacterial strains and moderate antiparasitic activity against *Cichlidogyrus tilapia*.

Keywords: *Enantia chlorantha*; DFT; antimicrobial; Caspase-3; MCF-7 and HCT116 cell lines; *Cichlidogyrus tilapia*;, Palmatine, Jatrorrhizine

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Table S1: The data of compounds (**1-4**) and B92 pending docking in Caspase-3 (PDB ID: 3KJF) active spots.

Caspase-3					
Comp	Energy score (S) (Kcal/mol)	Affinity Bond strength (Kcal/mol)	Affinity Bond length (in A°from the main residue)	Amino acids	Receptor functional group
1	-5.71	-0.3	3.16	Ala 254	-CH2-dihydroisoquinoline
		-2.2	1.94	Arg 207	OCH3
		-0.5	3.49		Phenyl of isoquinoline
		-0.2	3.44	Gly 122	=C H- phenyl of dihydro-isoquinoline
2	-5.58	-0.4	4.03	Cys163	OCH3
		-0.2	3.51		=CH- phenyl of dihydro-isoquinoline
		-0.2	3.29	His 121	
		-0.3	4.94		Phenyl of dihydro-isoquinoline
		-0.2	4.50	Met 61	Phenyl of isoquinoline
		-0.2	3.63	Glu 123	CH2-dihydroisoquinoline
		-0.2	3.29	Gly 122	=CH- phenyl of isoquinoline
					=CH- phenyl of isoquinoline
3	-5.61	-0.2	4.20	Tyr 204	CH2-dihydroisoquinoline
		-2.7	2.62	Ser 120	OH
		-0.2	3.58	Glu 123	=CH- phenyl of isoquinoline
		-0.2	3.26	Gly 122	=CH-phenyl of isoquinoline
4	-6.19	-0.4	4.20	Phe 256	-CH2-cyclopentane ring
		-0.8	3.14	Cys 163	OH
		-0.2	3.78		-CH2-phenanthrenol ring
		-1.1	2.92	His 121	OH
		-0.2	3.75		-CH2-phenanthrenol ring
B92	-6.38	-0.3	4.36	Phe 256	-CH2-cinnoline ring
		-0.6	4.81	Asn 208	Phenyl ring
		-2.7	3.08	Arg 207	C=O
		-0.4	3.31		OH
		-0.3	3.42	Cys 163	C=O
		-0.2	4.21		CH2-pentanoic acid
		-0.4	3.03	Thr 62	C=O

Table S2: Physicochemical properties of compounds (**1**-**4**) (TPSA, Lipinskis´ rule of five and Vebers´ rule,)

Cpd. No.	Number of HBD* <5	Number of HBA* <10	MlogP <4.15	M.W.* (g/mol) <500	RT*	TPSA*	Lipiniskis´ violations	Vebers´ violations
1	0	4	2.01	352.40	4	40.80	0	0
2	1	4	1.78	338.38	3	51.80	0	0
3	1	4	1.78	338.38	3	51.80	0	0
4	1	1	6.73	414.71	6	20.23	1: MLOGP>4.15	0

*HBD: Hydrogen bond donor, HBA: Hydrogen bond acceptor, M.W.: Molecular weight, RT= rotatable bond, TPSA: topological polar surface area, MLOGP= Moriguchi octanol-water partition coefficient.