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Chemical and biological activity of login: A DFT study

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Abstract
In this paper we optimized geometry of Logain with help of combination DFT/B3LYP method and 6-311G (d, p) basis set. QTAIM calculation shows that out of five interaction O18-H19 having highest interaction energy. The Chemical activity calculated with help of HOMO, LUMO and MESP of loganin. Docking of loganin by swissdock online server shows that PAPNON receptor is more effectively bind with logain as compare to PAPN2.Several biological activity also predicted by PASS software.

Keywords: QTAIM, PAPN2, PAPNON, DFT

Introduction
The old-fashioned medicine used for the management of liver disorders are very useful for documentation of the natural product which responsible for the hepatoprotection [1-3]. The monoterpene glucoside, loganin is byproduct in biosynthesis of corynanthe, Aspidosperma, Iboga, Cinchona, Ipecacuanha and pyrolochinolin alkaloids [4] known as monoterpene glucoside [5]. Loganin is one of the best-known of the iridoid glycosides. It is named for the Loganiaceae, having first been isolated from the seeds from member *Strychnos nux-vomica family* [6]. Here, in the present communication, we calculate chemical as well as biological activity of Loganin by using combination of DFT/B3LYP method and 6-311G (d, p) basis set. Nonlinear optical properties are also calculated by using same level theory. The purpose of this study assumes some modification in oxidation/reduction on polyfunctional bioactive natural product will generate new reactive sites in the molecule.

Computational Details
All calculation was done on my personal computer using combination of DFT/B3LYP method and 6-311G (d, p) [7-12] basis set without any symmetry constrain. In this calculation G03 software [13] is used for optimizing geometry [14]. AIMALL software is used to determined topological parameter and intermolecular hydrogen bonding [15]. Gauss view [16] is used for visualization optimized structure of logain. Chem craft 3.0 is used for graphics.

AIM Calculation
The logain shows Sofa type structure. The loganin contains three rings in which two are hexa and one is penta ring. In both hexa ring one carbon is replaced by oxygen. This oxygen contain two lone pair electron create antibonding repulsion so these ring slightly displaced from planarity. QTAIM calculations are done for the finding and description of hydrogen bonding within title molecule. In the outline of QTAIM, the hydrogen bonding is explored by presence of BCP between proton donor and acceptor atoms. QTAIM delivers a number of topological restrictions at BCP viz. charge density (ρBCP) and corresponding Laplacian ($\nabla^2\rho$BCP), kinetic energy density (G), potential energy density (V) and total energy density (H). Hydrogen bonds are characterized as weak and electrostatic in nature for $\nabla^2\rho$BCP> 0 H > 0 and for strong as well as covalent nature $\nabla^2\rho$BCP< 0 H < 0 at BCP [16]. According to our calculations, there exist five intra-molecular H-bonds in title molecule. Topological parameters associated with these H-bonds are listed in Table 2. Apparently, all H-bonds are found to be medium and weak. The interaction energy of H-bond can be calculated as E_{int} = ½ (VBCP) [17]. In our calculation O23-H35, O36—H38, O23-H22,O19-H18 are hydrogen bond with medium strength however O31-H28 hydrogen bond is weak strength.

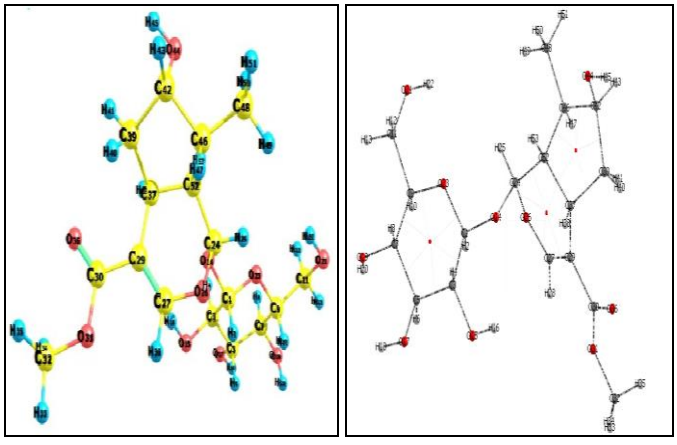


Fig 1: Molecular modeling and hydrogen bonding of Logain

Table 2: Topological parameters for bonds of interacting atoms: electron density (ρBCP), Laplacian of electron density (2ρBCP), kinetic electron energy density (*G*BCP), potential electron energy density (*V*BCP), total electron energy density (*H*BCP), estimated interaction energy (*E*int) at bond critical point (BCP).

O---H	ρBCP (a.u.)	$\nabla^2 \rho$bcp (a.u.)	*G*BCP (a.u.)	*V*BCP (a.u.)	*H*BCP (a.u.)	*E*int (kcal/mol)
O23-H35	.0127	.08124	-.0108	-.0109	-.0108	4.895
O36—H38	.0115	.0545	.0104	-.0929	-.0118	3.914
O23-H22	.0215	.0763	-.0113	-.0113	-.0231	3.623
O19-H18	.0183	.0531	.0131	-.0086	-.0118	4.931
O31-H28	.0165	.0654	-.0127	-.0105	-.0112	2.312

NLO Properties

Dipole moment (μ), polarizability<α>and total first static hyper polarizability β [18-21] are also calculated by using DFT/B3LYP method. They can be expressed in terms of *x*, *y*, *z* components and are given by following equations 1, 2 and 3-

$\mu = (\mu_x^2 + \mu_y^2 + \mu_z^2)^{1\backslash 2}$---------- (1)

$<\alpha> = 1\backslash 3\ [\alpha_{xx} + \alpha_{yy} + \alpha_{zz}]$ ---------- (2)

NLO properties described by [22-23] Hyperpolarizability of 3×3×3 matrix of third rank tensor. According to Kleinman symmetry 27 components of this 3x3x3 matrix contain can be summarized to 10 components [24]. The components of β are coefficients in the Taylor series expansion of the energy in the external electric field.

$E = E^0 - \mu_\alpha F_\alpha - 1/2\alpha_{\alpha\beta}F_\alpha F_\beta - 1/6\beta_\alpha\beta_\gamma F_\alpha F_\beta F_\gamma$

Where E^0 is the energy of the unperturbed molecules, Fα the field at the origin μ_α, $\alpha_{\alpha\beta}$, and $\beta_{\alpha\beta}$ are the components of dipole moment, polarizability and the first hyperpolarizabilities respectively

$\beta_{Total} = (\beta_x^2 + \beta_y^2 + \beta_z^2)^{1\backslash 2} = [(\beta_{xxx} + \beta_{xyy} + \beta_{xzz})^2 + (\beta_{yyy} + \beta_{yxx} + \beta_{yzz})^2 + (\beta_{zzz} + \beta_{zxx} + \beta_{zyy})^2]^{1\backslash 2}$--- (3)

The β components of Gaussian output are reported in atomic units. Where (1 a.u. =$8.3693X10^{-33}$e.s.u.

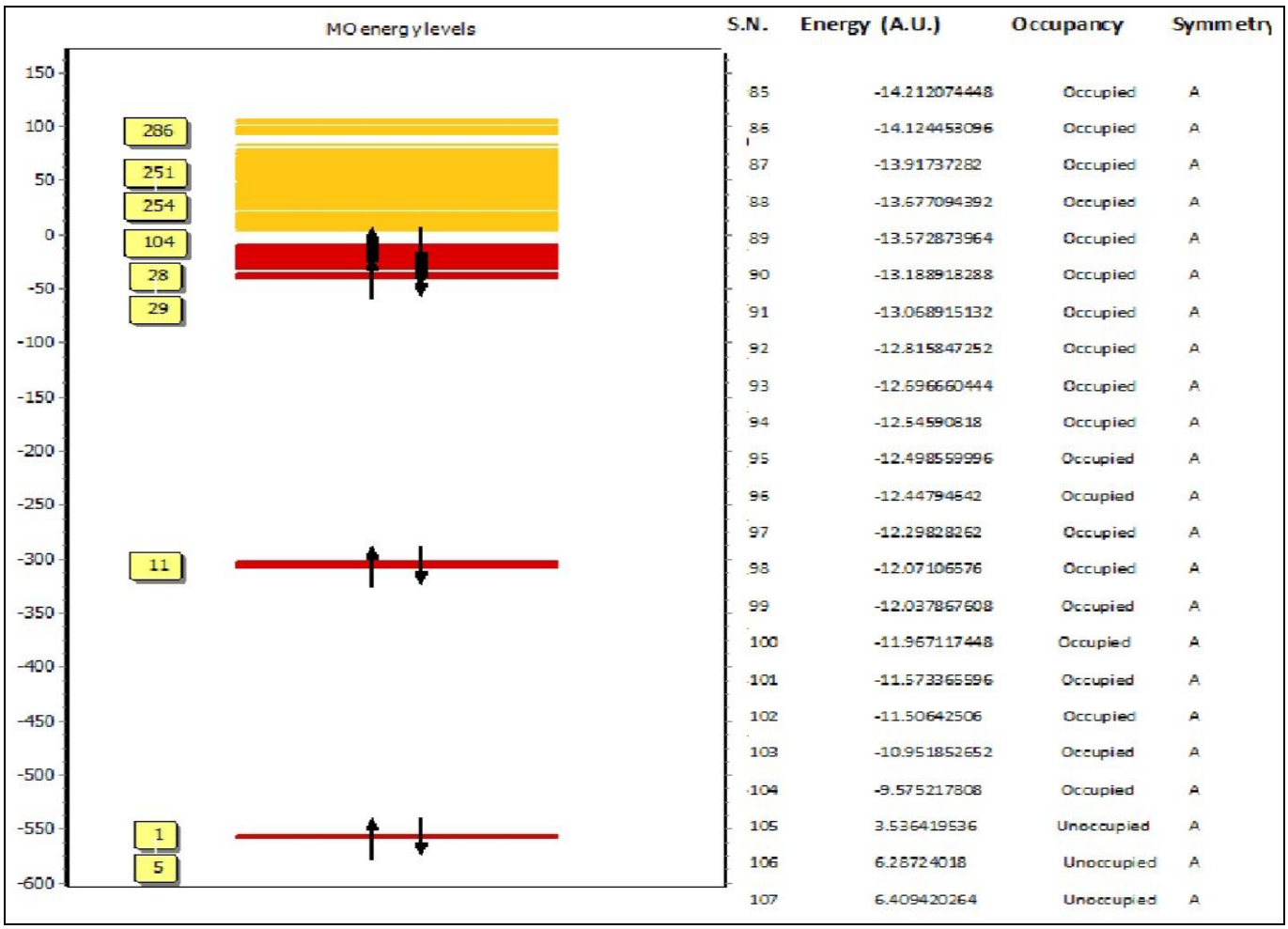
In logain calculated dipole moment value is 1.79.Debye. Logain having lower dipole moment as compared water (2.16 Debye), loganin can be used as better solvent. In polarizibility calculation greater contribution of α_{xx}, α_{yy}, α_{zz} which shows that molecule is elongated more towards, X,Y Z direction. Total hyper-polarizibility of title molecule is 51 times greater than Urea. So this shows that title molecule shows a good candidate for NLO.

Table 3: Polarizability& Hyper Polarizability of Title molecule

Polarizability		Hyper Polarizability			
α_{xx}	-150.9756	β_{xxx}	9.3337	β_{yzz}	-7.4348
α_{xy}	6.1855	β_{xxy}	-38.3861	β_{yyz}	-17.7589
α_{yy}	-165.0507	β_{xyy}	74.3994	β_{xyz}	-8.4032
α_{yz}	3.51	β_{yyy}	-64.0743	β_{total}	18.99
α_{zz}	-160.0213	β_{zzz}	14.1042		
α_{zx}	0.00	β_{xxz}	-39.3747		
A	79.845	β_{xzz}	-3.6339		

Electronic Properties

The interface with other types in a chemical system is also resolute by frontier orbitals, HOMO and LUMO. The frontier orbital gap helps to differentiate the chemical reactivity and kinetic stability of the molecule. The molecule which has a larger orbital gap is more polarized so more reactive far as reaction is concerted [25]. The frontier orbital gap in case of the loganin is 13.60eV. The contour plots of the HOMO, LUMO structure of the loganin are shown in Figure-3. HOMO and LUMO both located at ring R3. HOMO act primarily donor and LUMO act primarily acceptor. So HOMO-LUMO The importance of MESP lies in the fact that it simultaneously displays molecular size, shape as well as positive, negative, and neutral electrostatic potential region in terms of grading and is very useful in the investigation of molecular structure with its physiochemical property relationship [26-27]. The MESP diagram is shown in Figure 4. Arrangement of occupied and unoccupied orbitals according to increasing energy value are shown in fig-2



S.N.	Energy (A.U.)	Occupancy	Symmetry
85	-14.212074448	Occupied	A
86	-14.124453096	Occupied	A
87	-13.91737282	Occupied	A
88	-13.677094392	Occupied	A
89	-13.572873964	Occupied	A
90	-13.188918288	Occupied	A
91	-13.068915132	Occupied	A
92	-12.815847252	Occupied	A
93	-12.696660444	Occupied	A
94	-12.54590818	Occupied	A
95	-12.498559996	Occupied	A
96	-12.44794542	Occupied	A
97	-12.29828262	Occupied	A
98	-12.07106576	Occupied	A
99	-12.037867608	Occupied	A
100	-11.967117448	Occupied	A
101	-11.573365596	Occupied	A
102	-11.50642506	Occupied	A
103	-10.951852652	Occupied	A
104	-9.575217808	Occupied	A
105	3.536419536	Unoccupied	A
106	6.28724018	Unoccupied	A
107	6.409420264	Unoccupied	A

Fig 2: Arrangement of MO according to increasing Energy level

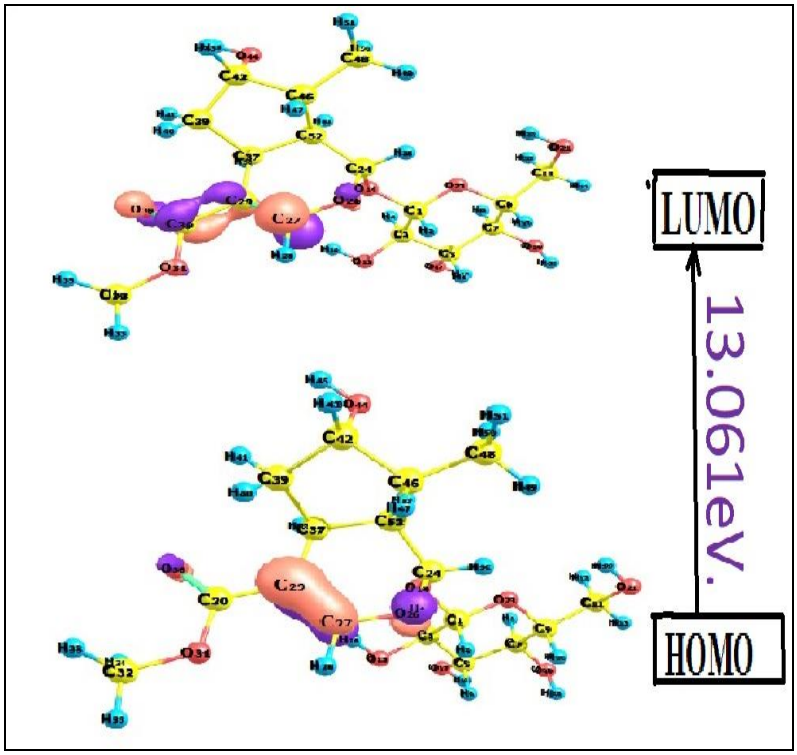


Fig 3: HOMO-LUMO Plot of Logain

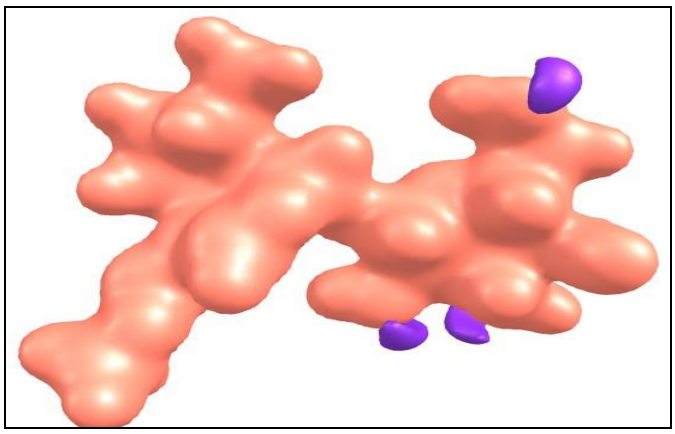


Fig 4: MESP Plot of Logain

Biological Activity

PASS (prediction of activity spectra) [28] is an online server based on the structure of a compound uses to predicts almost 900 activities. According to PASS analysis antidyskinetic activity for the logain with *P*a (probability to be active) value of 0.886. From calculated activity Mucomembranous protector value. 842 shows title compound inhibit any bacteria inside mucus and protect cell for liver disorder. Loganin sows activity for Anti-seborrheics (0.891) are drugs effective in seborrheic dermatitis (dandruff) [29]. Selenium sulfide, zinc pyrithione, corticosteroids, imidazole antifungals, and salicylic acid are common anti-seborrheics. Selenium sulphide recognized to reduce aridness of scalp and folliculitis perform as an anti-keratolytic [30]. This is noted that whole toxicity can appear if this is applied to exasperated skin. Logain inhibits any toxicity in case of bacterial attack on exasperated skin. Title compound is active against CYP2C12 substrate. CYP2C12 gene goes to cytochrome family whose appearance is liver-specific and controlled at the transcriptional level by evolution hormone [31]. Designing new antidyskinetic agents wants the empathy of targets which when repressed can kill the effected cells. PAPNON and PAPN2 receptor is recognized as an efficient target, for interaction with Loganin. To execute this the molecular docking simulation of the Logain with PAPNON and PAPN2 receptor could done by Swiss dock online server. The three dimensional (3D) structure of protein was found from Protein Data Bank (PDB ID: 3PBL). Thymidylate kinase (PAPN2) 60-fold abridged phosphorylation rate of azidothymidine (AZT) monophosphate (AZTMP), the partially activated AZT metabolite, by human thymidylate kinase (TMPK) severely limits the efficacy of this anti-HIV drug. Crystal structures of different TMPK nucleotide complexes show that steric hindrance by the azido group of AZTMP which prevents formation of the catalytically active closed conformation of the P-loop of TMPK. The configuration of HEMOGLOBIN (VAL BETA1 MET, TRP BETA37 TYR) MUTANT (PAPNONE) is deoxy forms of four recombinant hemoglobins in which Trp37 (C3) beta is substituted with Tyr (betaW37Y), Ala (betaW37A), Glu (betaW37E), or Gly (betaW37G). Swiss Dock can analyse protein-ligand docking, supercilious the legend is rigid, and it can overlay pairs of molecule using only information of their 3D shapes. The docking score can be approached to an interaction energy value (*e*-value), which we pursue to minimize. As negative the *e*-value increases the efficient will be the docking process increases. We have computed molecular docking to get understanding into the potential target of PAPNON and PAPN2 receptor for binding with logain. Memorandum that it is just a model that may deliver the binding affinity of a specific spot in terms of *e*-value. The docking of title compounds PAPNON and PAPN2 receptor is showed in Figure 4. The total *e*-value obtained is −2331.83A.U. for PAPNON and −1655.497A.U. for the PAPN2. This result shown that that PAPNON is more effectively bind than PAPN2 with Logain.

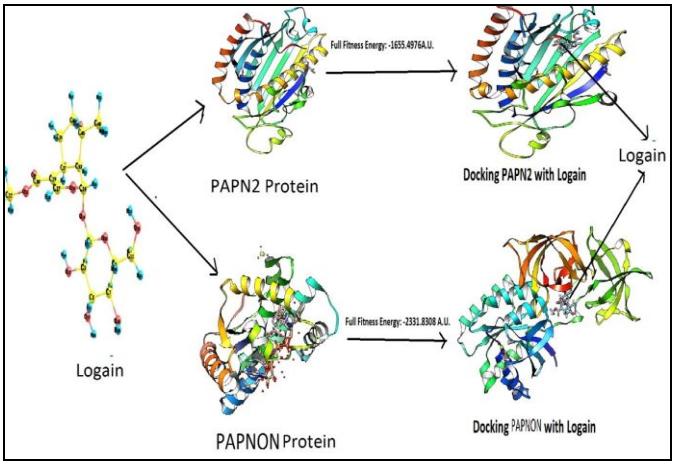


Fig 5: Docking of PAPNON and PAPN2 Protein with Logain

Table 2: Biological Activity parameter of Loganin Pa>.70

S. No	Activity	Probability
1	Mucomembranous protector	0.842
2	Anesthetic general	0.802
3	Antiseborrheic	0.891
4	Sugar-phosphatase inhibitor	0.837
5	Ubiquinol-cytochrome-c reductase inhibitor	0.788
6	Aspulvinone dimethylallyltransferase inhibitor	0.928
7	CYP2C12 substrate	0.886

Conclusion

In this paper we study chemical and biological activity of logain calculated by combination of DFT/B3LYP method and 6-311G (d, p) basis set. Hydrogen bonding and other topological parameter of Logain calculated with help of AIMALL software. In these studies our finding indicates that out of five intermolecular interactions four are medium strength. Biological activity shows that PAPNON is more effective bind with logain as compare to PAPN2.

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