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Molecular Docking and ADMET Studies of some Secondary Metabolites from Buchholzia Coriacea which Target Inos and COX-2 related to Paracetamol Hepatotoxicity

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Abstract

Paracetamol (N-acetyl-p-aminophenol; APAP) is a widely used over-the counter analgesic and antipyretic drug, overdose of APAP leads to hepatotoxicity. *Buchholzia coriacea* plant is useful in folk's medicine for the treatment of a wide range of diseases due to its secondary metabolites. The molecular interaction and ADMET analysis (*in-silico* study) of *B. coriacea* compounds and APAP hepatotoxicity targeted proteins were evaluated in this study. Inducible nitric oxide synthase (iNOS) and Cyclo-Oxygenase-2 (COX-2) are the two proteins that were considered for the purpose of this research. The complete modeling of the proteins has allowed the identification of new molecular target in the treatment of APAP hepatotoxicity. Active molecular docking using Schrödinger Suite revealed that the following secondary metabolites: quercetin, catechin, ellagic, narigenin and Butein exhibited high binding affinities towards iNOS and COX-2 compared to N-Acetylcyeteine (NAC), a known APAP antihepatotoxic standard drug which had the lowest binding affinity. The ADMET properties of the phytochemicals analyzed from *B. coriacea* were evaluated to explain their pharmacokinetic properties using Qikprop. The results of ADMET analysis showed that Butein and Biochanin A sailed through the 8 parameters of ADMET analysis successfully. The result indicated that biochanin A and butein exhibited good affinities to bind iNOS and COX-2 by interacting at the catalytic site of the proteins. Hence the isolation of these secondary metabolites from *B. coriacea* seed extract may be a potential lead compounds for the management of APAP hepatotoxicity but further experimental and clinical verification is needed to establish them as antihepatotoxic drug.

Keywords: Affinity; Secondary metabolites; Pharmacokinetic; Catalytic; Hepatotoxicity.

Introduction

Acetaminophen

Acetaminophen (paracetamol, N-acetyl-p-aminophenol) abbreviated as APAP is a widely used over-the-counter analgesic and antipyretic drug, safer at 1 g per single dose or 4 g per day for adult human being; however, overdose produces potentially fatal hepatic centrilobular necrosis [14]. APAP poisoning has been a significant clinical problem since widespread therapeutic use began in 1970s. APAP overdose is leading cause of hepatic failure in USA, Europe, and Australia. APAP poisoning accounts for approximately one half of all cases of acute liver failure in USA and Great Britain today [20] and is metabolized primarily by conjugation with glucuronic acid and sulfate in liver of many species. Less than 5% of the dose is metabolized by hepatic cytochrome P-4502E1 to N-acetyl-p-benzoquinone imine (NAPQI), a chemically reactive metabolite. At therapeutic doses, this metabolite is efficiently detoxified by glutathione in liver. At large doses, NAPQI production exceeds GSH detoxification capacity; NAPQI covalently binds to various cell proteins to

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form inactive conjugates [13]. These conjugates can lead to irreversible hepatic cell injury and liver necrosis. By various mechanisms, NAPQI can bind to SH groups of enzymes and may contribute to metabolic alteration in liver [30]. While there is strong evidence that metabolic activation of acetaminophen to NAPQI is a prerequisite for development of toxicity, more recent investigation has focused on interplay of inflammatory mediators involved in the progression of APAP-induced injury, both to further the understanding the mechanism of APAP induced injury and to identify possible therapeutic targets for late-presenting patients [15,18,19].

Acetaminophen-induced hepatotoxicity

Davidson and Eastham were the first to report that acetaminophen was hepatotoxic in overdose [5]. They described two individuals who developed hepatotoxicity following acetaminophen overdose and died on the third day. Liver injury induced by APAP overdose is manifested as extensive centrilobular necrosis, infiltration of inflammatory cells and bleeding. Hepatocellular necrosis is initiated by a reactive metabolite, N-Acetyl-P-Benzoquinone imine (NAPQI), mainly produced by cytochrome P450 2E1 [12]. Microscopic examination of liver sections from these individuals indicated fulminating hepatic necrosis. The necrosis was primarily in the centrilobular areas.

N-acetyl cysteine (The standard drug)

N-Acetyl-Cysteine (NAC) can be an effective antidote for APAP poisoning. NAC limits hepatotoxicity by increasing GSH synthesis in the liver [24]. Current protocols recommend treating patients with an initial dose of 150 mg/kg NAC, infused over a period of an hour, upon hospitalization, followed by decreasing amounts of NAC infused over the next 20 hours [3]. Fatal liver damage can be prevented if the initial dose of NAC is administered within 8-12 hours of an APAP overdose. This antidote dosage regime has been developed empirically over a period of many years based on outcomes from clinical cases.

***Buchholzia coriacea* plant**

Buchholzia coriacea is a forest tree with large glossy leathery leaves and conspicuous cream white flowers at the end of its branches. Its leaves and stem bark in various formulations, decoctions and concoction exhibit anti-helmintic, antimicrobial and cytotoxic effects on micro-organism [1,8]. In folklore medicine, the seed of *B. coriacea* is used in the treatment of pain and inflammatory conditions such as asthma, rheumatism and ulcer. The wide range of the acclaimed effects of the seed of this plant earned it the name 'wonderful kola'.

Buchholzia coriacea was named after Reinhold Wilhelm Buchholz who collected the plants in Cameroon in the late 19th century [2]. It belongs to the family *Capparidaceae*. The family *capparidaceae* is described from Carpe Verde Islands. It comprises of 45 genera and approximately 1000 species, distributed in the tropical and sub-tropical regions, especially east Africa and South America. The plant is an evergreen under-storey tree of lowland rainforest, up to 20 meters high occurring in Cameroon, Congo, Central African Republic, Gabon, Angola, Nigeria, and Ghana among others [2]. It is a shrub or medium-sized tree, evergreen, with a dense crown, large, glossy, leathery leaves arranged spirally and clustered at the ends of the branches and conspicuous cream-white flowers in racemes at the end of the branches [7]. The bark of the plant is smooth, blackish-brown/dark-green. Slashes are deep red turning dark brown. The leaflets are large, obviate, oblanceolate to elliptic, shortly acute at apex, cuneate at base, $15x30x5^{-11}$ cm, thinly coriaceous, glabrous, midrib very prominent below, stalk 10-15 cm long, swollen for about 1 cm at the both ends, pale green [6]. The fruits are large, long stalked, ellipsoid, resembling, avocado peas, $12x15^{-8}$ cm, endocarp up to 1.3 cm thick and woody, yellowish when ripe, flash yellow, edible, containing a few large blackish seeds about 2.5 cm long.

There is however a dearth of scientific information on the analgesic and anti-inflammatory activity of *B.coriacea*. This study therefore sought to investigate, *in-silico*, the analgesic and anti-inflammatory properties of *B. coriacea*.

Materials and methods

Protein preparation

In order to perform molecular docking analysis, at first, retrieval of the three-dimensional crystal structure of the human inducible nitric oxide synthase (PDB ID 4NOS) and human cyclo-oxygenase-2 (PDB ID 5KIR) in PBD format from the protein data bank were accomplished. Protein Preparation Wizard of Schrödinger Maestro v9.4 was used for the preparation and refinement of the downloaded proteins (Dash et al., 2015). Charges and bond orders were assigned and water molecules were deleted. Hydrogen was added to the heavy atoms. Energy minimization was done by using OPLS 3 force field by fixing the heavy atom RMSD of 0.30Å (Shivakumar et al., 2010). Amino acids were optimized by using neutral pH.

Ligand preparation

From the Pubchem database the 2D structure of the of the phytochemicals analysed from the plant such as quercetin, ellagic, biochanin A, catechin, butein, narigenin and other phytochemicals were downloaded. Ligand preparation was done to create three dimensional geometries and to assign proper bond orders [23]. Three dimensional geometries were generated by using Ligprep2.5 in Schrödinger Suite 2013 with an OPLS-3 force field [26]. For the generation of ionization states, we used Epik2.2 in Schrödinger Suite at pH7.0±2.0 [29]. A maximum of 32 possible stereoisomers per ligand were obtained.

Receptor grid generation

During docking trajectory every poses binds to the predicted active site that's why receptor grids were calculated for the prepared protein. For Glide docking, grids were generated by using OPLS-3 force field by keeping the Van-der Waals scaling factor of 1.0 and charge cut off value of 0.25. A box was generated to each direction with 14Å × 14Å × 14Å for docking experiments.

Extra Precision (XP) ligand docking

XP ligand docking was performed rather than SP docking because XP is better than SP in scoring function and it also predicts the false positive results [9]. This docking was performed in Glide of Schrödinger Maestro v9.4 [10]. Final result of docking can be found as glide score by energy minimization. For docking, Van-der Waals scaling factor was set to 0.85 and 0.15 for ligand compounds and partial charges cut off value was fixed at -10.0 kcal/mol. The lowest glide score containing compounds were then subjected to MM-GBSA analysis for binding free energy calculation and best poses were recorded for every ligand compounds.

Prime MM-GBSA: Binding free energy calculation was also carried out for the protein ligand complexes. MM-GBSA is a

combined method for binding free energy calculation which was used in this experiment that accumulates OPLSAA molecular mechanics energies (EMM), an SGB solvation model for polar solvation (GSGB), and a non-polar solvation term (GNP) composed of the non-polar solvent accessible surface area and Van-der Waals interactions [22]. The best poses from the Glide score were used for binding free energy calculation. The total free energy of binding: $\Delta G_{bind} = G_{complex} - (G_{protein} + G_{ligand})$, where G = EMM + GSGB + GNP.

Ligand based ADMET analysis

For the analysis of physiological descriptors of a compound such as adsorption, distribution, metabolism and excretion behavior of the ligand compounds ADMET analysis was done in QikProp module of Schrodinger [21]. It also predicts the physicochemical nature of the compounds as well as their pharmacokinetics properties. In this study, we used the Qikprop 3.2 module of Schrodinger [25]. There are also several other descriptors also analyzed such as Predicted IC_{50} for blocking HERG K^+ channel *in vitro*, predicted octanol or water partition coefficient [log P(o/w)], number of Hydrogen Bond Acceptors (HBA), number of Hydrogen Bond Donors (HBD), predicted aqueous solubility (log s), Solvent-Accessible Surface Area (SASA), skin permeability (log Kp), MDCK cell permeability (MDCK), binding to human serum albumin (log Khsa), blood-brain partition coefficient (log BB), percentage human oral absorption rate.

Table 1: Docking score of inducible nitric oxide synthase (Inos) with the secondary metabolites analysed from *B. Coriacea* and Nac.

	Inducible nitric oxide synthase receptor	
S/N	Compounds	Docking Score (Kcal/Mol)
1	Quercetin	-7.005
2	Catechin	-6.64
3	Ellagic	-5.498
4	Narigenin	-5.449
5	Butein	-5.011
6	Gallic acid	-4.988
7	Apigenin	-4.366
8	Coumaric acid	-3.749
9	Caffeic acid	-3.679
10	Biochanin A	-3.662
11	Beta sitosterol	-3.233
12	Hexadecanoic acid methyl ester	-2.876
13	N-Acetylcysteine (NAC, Standard drug)	-2.86

Results

WHERE;

Total solvent accessible surface area, SASA = 300.0-1000.0

Hydrogen bonds donor, HB donor = 0.0-6.0

Hydrogen bonds acceptor, HB acceptor = 2.0-20.0

Predicted IC_{50} value for blockage of HERG K^+ channels, QPlogHERG = Concern below -5

Predicted qualitative human oral absorption, HOA(%) = >80% is high, <25% is poor

Table 2: Docking score of Cyclooxygenase 2 (Cox-2) with the Co-Ligand, the secondary metabolites analysed from *B. Coriacea* and Nac.

	Cyclooxygenase-2 Receptor	
S/N	Compounds	Docking Score (Kcal/Mol)
1	CO-Ligand (Rofecoxib)	-9.681
2	Quercetin	-8.738
3	Catechin	-7.504
4	Ellagic	-9.818
5	Narigenin	-7.464
6	Butein	-8.994
7	Gallic acid	-7.007
8	Apigenin	-7.206
9	Coumaric acid	-4.93
10	Caffeic acid	-6.206
11	Biochanin A	-7.755
12	Beta sitosterol	-6.234
13	Hexadecanoic acid methyl ester	-3.791
14	Acetyl-cysteine (Standard drug)	-3.59

Table 3: Admet properties of some secondary metabolites analysed from *B. Coriacea* using qikprop.

S/N	Compounds	SASA	DonorHB	AccptHB	QPlog Po/w
1	1-(10)-Ascorbic-acid-2, 6-dihexadecanoate	1376.372	2	9.95	9.152
2	2-Methyl-pyrrolidine-2-carboxylic	324.05	2	3	-1.527
3	Acetyl-cysteine (Standard drug)	357.131	1.25	3.25	0.562
4	Apigenin	490.278	2	3.75	1.607
5	Beta sitosterol	771.178	1	1.7	7.621
6	Biochanin A	509.656	1	3.75	2.543
7	Butein	523.538	3	4	1.351
8	Caffeic acid	388.863	3	3.5	0.545
9	Campesterol	752.659	1	1.7	7.301
10	Catechin	512.552	5	5.45	0.45
11	Coumaric acid	377.068	2	2.75	1.425
12	Docosanoic acid	869.621	1	2	7.605
13	Eicosanoic acid	802.732	1	2	6.816
14	Ellagic	455.912	4	8	-1.294
15	Estra-1,3,5[10]-triene-17-beta-ol	634.004	1	2.45	5.282
16	Ferulic acid	417.5	2	3.5	1.371
17	Gallic acid	341.645	4	4.25	-0.578
18	Hexadecanoic-acid-15-methyl-methylester	747.762	0	2	6.132
19	Hexadecanoic acid	670.475	1	2	5.307
20	Hexadecanoic acid methyl ester	711.001	0	2	5.788
21	Lupeol	695.269	1	1.7	7.111
22	Narigenin	498.135	2	4	1.623
23	Phenol-3,5-bis(1,1-dimethylethyl)	754.183	3	0.75	7.795
24	Piperic acid	428.216	1	3.5	2.189
25	Stigmasterol	756.449	1	1.7	7.5

Predicted blood/brain partition coefficient, QPlogBB = -3.0-1.2

Predicted value for serum protein binding $QPlogK_{Hsa}$

Predicted octanol/water partition coefficient, QPlog Po/w = -2.0-6.5

Result of molecular interaction of the co-Ligand, the standard drug (Nac) and the secondary metabolites analysed from *B. Coriacea* with inducible nitric oxide synthase receptor (Inos)

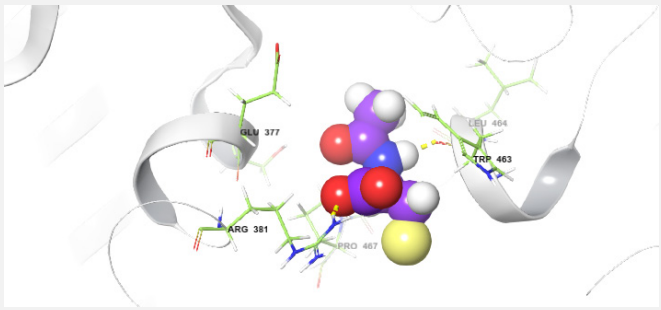

Figure 1: Molecular interaction of n-acetly cysteine with inducible nitric oxide synthase receptor.

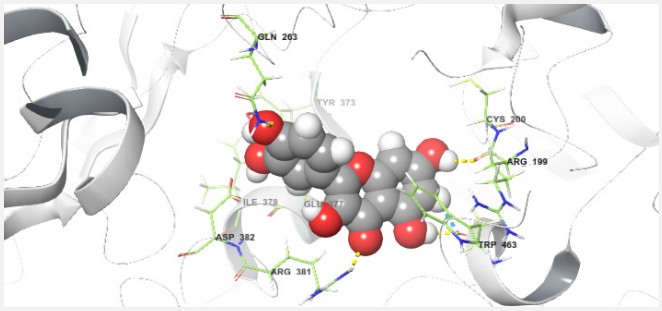

Figure 2: Molecular interaction of quercetin with inducible nitric oxide synthase receptor.

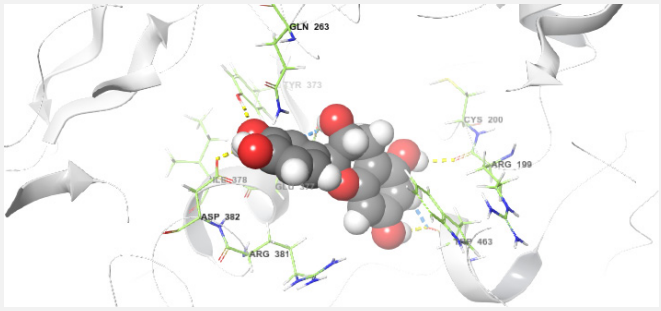

Figure 3: Molecular interaction of catechin with inducible nitric oxide synthase receptor.

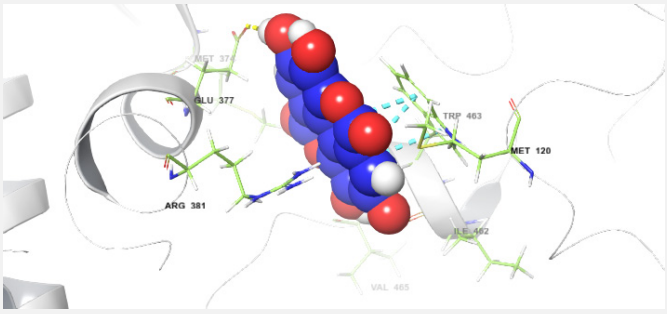

Figure 4: Molecular interaction of ellagic with inducible nitric oxide synthase receptor.

Table 4: Admet properties of some secondary metabolites analysed from B. Coriacea using qikprop.

S/N	Compounds	QPlog HERG+	QPlogBB	QPlog-Khsa	%HOA
1	1-(10)-Ascorbic-acid-2, 6-dihexadecanoate	-7.33	-4.63	1.792	92.917
2	2-Methyl-pyrrolidine-2-carboxylic	-1.369	0.106	-0.731	50.027
3	Acetyl-cysteine(Standard drug)	0.238	-0.648	-1.087	62.782
4	Apigenin	-5.115	-1.447	-0.038	73.194
5	Beta sitosterol	-4.669	-0.353	2.076	100
6	Biochanin A	-5.121	-0.881	0.091	90.608
7	Butein	-5.407	-2.184	-0.254	65.66
8	Caffeic acid	-2.169	-1.546	-0.804	54.29
9	Campesterol	-4.646	-0.291	1.978	100
10	Catechin	-4.778	-1.916	-0.415	59.997
11	Coumaric acid	-2.253	-1.074	-0.67	67.46
12	Docosanoic acid	-4.176	-2.005	1.308	100
13	Eicosanoic acid	-3.904	-1.823	1.046	96.517
14	Ellagic	-3.842	-2.395	-0.658	35.438
15	Estra-1,3,5[10]-triene-17-beta-ol	-4.627	-0.133	1.181	100
16	Ferulic acid	-2.239	-1.175	-0.612	67.242
17	Gallic acid	-1.413	-1.667	-0.985	41.39
18	Hexadecanoic-acid-15-methyl-methylester	-5.49	-0.996	1.153	100
19	Hexadecanoic acid	-3.293	-1.375	0.533	88.968
20	Hexadecanoic acid methyl ester	-5.275	-0.884	0.976	100
21	Lupeol	-3.789	0.11	2.036	100
22	Narigenin	-4.976	-1.402	-0.031	74.266
23	Phenol-3,5-bis(1,1-dimethylethyl)	-3.998	-0.299	1.972	100
24	Piperic acid	-2.335	-0.693	-0.478	81.185
25	Stigmasterol	-4.526	-0.282	2.066	100

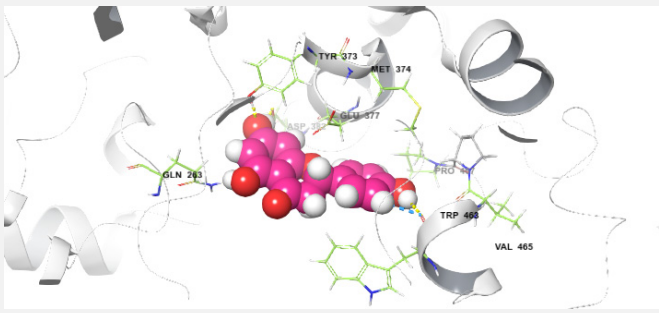

Figure 5: Molecular interaction of narigen in with inducible nitric oxide synthase receptor.

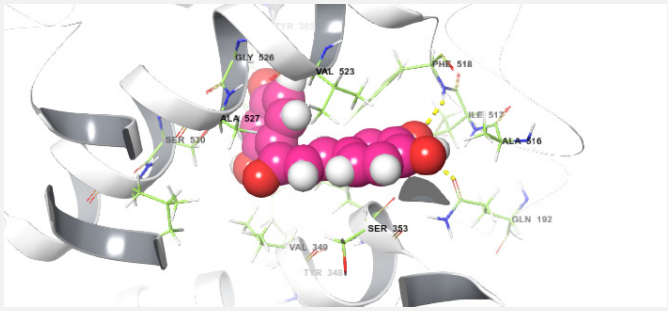

Figure 6: Molecular interaction of Bute in with inducible nitric oxide synthase receptor.

Results of molecular interaction of the co-ligand, the standard drug (Nac) and the secondary metabolites analysed from *B. Coriaceae* with cyclooxygenase-2 receptor (Cox-2)

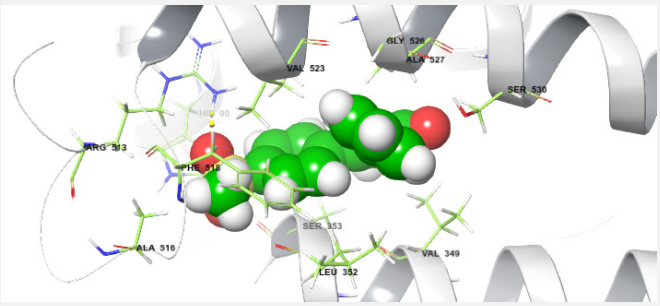

Figure 7: Molecular interaction of co-ligand (rofecoxib/rcx) with cyclo-oxygenase 2 receptor.

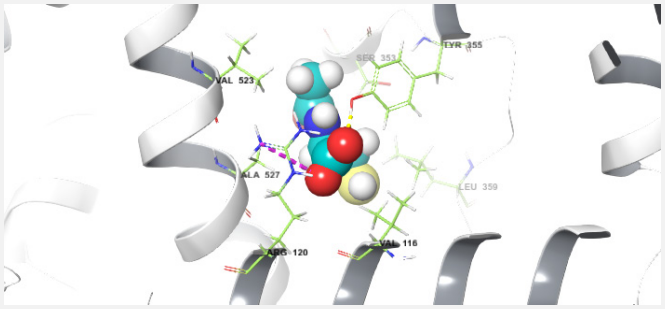

Figure 8: Molecular interaction of n-acetyl-cysteine with cyclo-oxygenase 2 receptor.

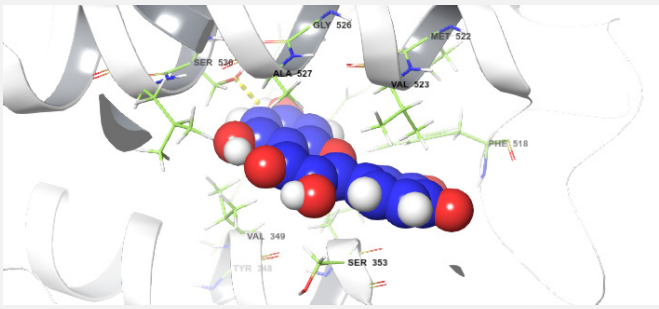

Figure 9: Molecular interaction of quercetin with cyclo-oxygenase 2 receptor.

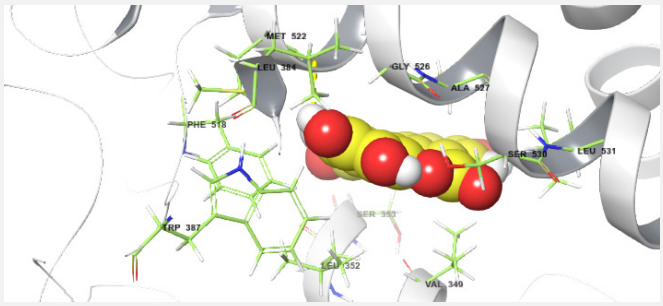

Figure 10: Molecular interaction of ellagic with cyclo-oxygenase 2 receptor.

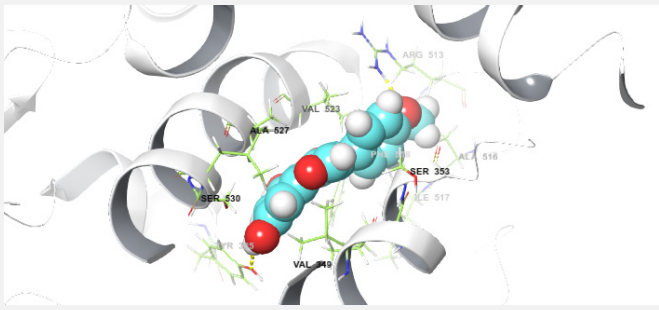

Figure 11: Molecular interaction of biochanin a with cyclo-oxygenase 2 receptor.

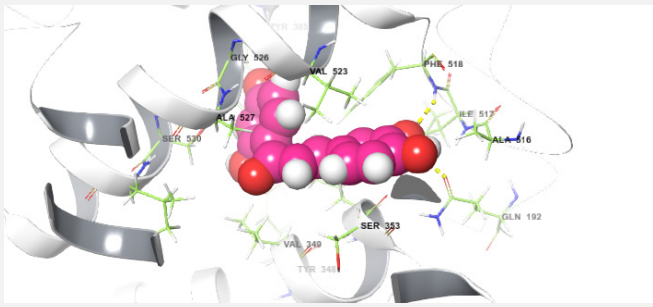

Figure 12: Molecular interaction of Bute in with cyclo-oxygenase 2 receptor.

Discussion

Inducible nitric oxide synthase receptor: Inducible Nitric oxide is a highly reactive oxidant produced by liver parenchymal and nonparenchymal cells from L-arginine via an inducible form of Nitric Oxide Synthase (iNOS). Previous studies have shown that nitric oxide also contributes to the hepatotoxicity of endotoxin, like acetaminophen induces a marked accumulation of macrophages in the liver using Aminoguanidine, a relatively selective inhibitor of iNOS blocked acetaminophen-induced hepatotoxicity [14,17]. However, in another study, inhibition of iNOS by amino-guanidine resulted in reduced APAP hepatotoxicity. These findings support the concept that nitric oxide plays a role in liver injury associated with inflammation [11]. The present studies were designed to examine the potential role of nitric oxide in the pathophysiology of acetaminophen induced hepatotoxicity. From this research, the binding affinity of N-acetyl-cysteine used in the treatment of Acetaminophen toxicity was compared with other ligands of the compounds derived from the plant *B. coriacea*. After docking of the phytochemicals with iNOS they possess binding affinities of, Quercetin (-7.005 kcal/mol) was observed to have the highest binding affinity followed by Catechin (-6.64 kcal/mol), Ellagic (-5.498 kcal/mol), Narigenin (-5.449 kcal/mol) and also Butein (-5.011 kcal/mol) and as a result of these make them exhibit anti-toxicant properties compared to N-acetyl-cysteine the standard drug which has lowest binding affinity of -2.86 kcal/mol. Other ligand exhibited low binding affinities to the receptor therefore they may not be a good potent lead in the management of APAP hepatotoxicity.

Cyclo-oxygenase-2 receptor: Cyclo-oxygenase-2 or COX-2, is an enzyme that in humans is encoded by the PTGS2 gene. In humans it is one of two cyclooxygenases. It is involved in the conversion of arachidonic acid to prostaglandin H2, an important precursor of prostacyclin, which is expressed in inflammation [28]. The two isoforms of Cyclooxygenase (COX) catalyze committed steps in the synthesis of a number of important Pros-

taglandin (PG) and thromboxane mediators [27]. Constitutively expressed COX-1 produces low-level PGs needed to maintain normal physiological functions, including platelet aggregation, whereas COX-2 is widely accepted to be the inducible form with a role in inflammatory processes [27]. From this study, the binding affinity of N-acetyl-cysteine used in the treatment of Acetaminophen toxicity was compared with other ligands of the compounds derived from the plant *B. coriacea*. After docking, it was observed that Ellagic have the highest and good binding affinity of -9.818 kcal/mol followed by Butein (-8.994 kcal/mol), Quercetin (-8.736 kcal/mol), Biochanin A (-7.755 kcal/mol), Catechin (-7.504 kcal/mol) compared to the standard drug N-acetyl-cysteine which has lowest binding affinity of -3.59 kcal/mol. The result showed that the compound derived from the plant may function well as the inhibitor of the targeted protein (COX-2) which make them exhibit the anti-inflammatory properties [8]. Also, Ellagic has higher binding affinity compared to the co-ligand (Rofecoxib) which has binding affinity of -9.681 kcal/mol [16].

Admet analysis: The ADMET properties of the phytochemicals analyzed form the plant *B.coriacea* were evaluated to explain their pharmacokinetic properties. Tables 3 & 4 illustrate ADMET properties of these compounds. The properties represent the bioavailability, distribution, cell permeability, excretion and absorption quality of the compounds. From the results of ADMET analysis, it was observed that, the blood brain barrier permeability of the tested compounds was nearly between the acceptable ranges which is very important for a drug to pass through those barriers. Ellagic, butein, catechin, narigenin and biochanin A showed QPlogBB value of -2.395, -2.814, -1.916, -1.402 and -0.881 respectively which are good, where the acceptable range is -3.0 to 1.2. The secondary metabolites: catechin, ellagic, butein, narigenin and biochanin A showed the number of hydrogen bonds donor value of 5, 4, 3, 2 and 1 respectively where acceptable range is 0.0-6.0 and also showed the number of hydrogen bonds acceptor value of ellagic (8), catechin (5.45), butein and narigenin (4) and biochanin A (3.75) which are in the value of acceptable range (2.0-20.0). Butein, catechin, biochanin A, narigenin and ellagic showed Solvent-accessible surface area value of 523.538, 512.552, 509.656, 498.135 and 455.912 respectively where the acceptable range value is 300.0-1000.0. Predicted IC_{50} value for blocking Human Ether-a-go-go Related Gene (HERG) K^+ channel were very close to the acceptable range (below -5) for both butein (-5.407) and biochanin A (-5.115). The predicted octanol or water partition coefficient for the Phyto-compounds were also analyzed, biochanin A, narigenin, butein, catechin and ellagic showed good predicted octanol or water partition coefficient by providing the acceptable value of 2.543, 1.623, 1.351, 0.45 and -1.294 respectively, where the acceptable range is -2.0 to 6.5. Human oral absorption rate was greater for biochanin A (90%) than narigenin (70%), butein (65%), catechin (60%) and ellagic (35%) where the acceptable percentage <25% is poor and >80% is good, therefore, the result indicated that human oral absorption of the selected secondary metabolites is good according to the findings of this study. After subjecting the selected five secondary metabolites, butein and biochanin A were the only secondary metabolites that were able to scale through the eight ADMET analysis parameters successfully because of their ability to block HERG K^+ channel.

Conclusion

The use of natural products has been widely use for the treatment of different diseases due to their structure and target diversity in the strategies used in the drug discovery processes and drug development when compared with synthetic drugs. Inducible nitric oxide synthase and cyclooxygenase-2 are important metabolic regulators processes for acetaminophen toxicity. They have been shown as potential pharmaceutical targets in this study.

In this research, the secondary metabolites of *B. coriaceae* plant were used for the protein targets antagonists, in which they possess high and good binding affinities to the protein targets, which is a new approach that are to be used in the management of acetaminophen hepatotoxicity. Also, ADMET analysis of the compounds derived from the plant were evaluated. After subjecting the selected 5 secondary metabolites, butein and biochanin A were the only secondary metabolites that are able to sail through the 8 ADMET analysis parameters successfully because of their ability to block HERG K^+ channel. Hence, they could be a potential drug in the management of paracetamol toxicity.

Wet research should be carried out to validate the result and biosafety of the secondary metabolites-butein and biochanin A-to fully establish them as better standard drugs with little or no side effects for the management of APAP hepatotoxicity.

Declarations

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