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MOLECULAR DOCKING STUDIES OF THE COMPOUNDS FROM *PERGULARIA DAEMIA* AND *TERMINALIA CATAPPA* L. LEAF EXTRACTS WITH CYP2E1,GST,UDP-GLUCURONYL TRANSFERASE AND Nrf_2 BINDING SITE IN KEAP1, IL-6

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Keywords:

Pergularia daemia, *Terminalia catappa*, CYP2E1, UGT, GST

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ABSTRACT: Objective: *Pergularia daemia* and *Terminalia catappa* L. Leaf extracted with hydroethanol and the extracts were separated by silica gel column chromatography. The selected column fractions are used in GC-MS analysis, from the GC-MS results eight phytochemical compounds are selected based on their biological activities. In the present work we predict the interaction of the selected targeted proteins (CYP2E1, UDP-GT, GST and Nrf_2 binding site in keap1 protein,IL-6) with bioactive compounds of the extracts (HAEPD and HAETC) by molecular docking studies. The number of bioactive compounds present in HAEPD and HAETC, and there phytochemicals are responsible for various biological as well as hepatoprotective and anti hepatotoxic properties of the plant extracts.

INTRODUCTION: Medicinal plants are believed to be an important source of new chemical substances with potential therapeutic effects [1]. Medicinal plants have been identified and used throughout human history. Plants have the ability to synthesize a wide variety of chemical compounds that are used to perform important biological functions, and to defend against attack from predators such as insects, fungi and herbivorous mammals [2]. The term medicinal plants include various types of plants used in herbalism and some of these plants have a medicinal activities. Medicinal plants are the "backbone" of traditional medicine, which means more than 3.3 billion people in the less developed countries utilize medicinal plants on a regular basis [3].

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Many metabolites have been found to possess interesting biological activities and find applications, such as pharmaceuticals, insecticides, dyes, flavors and fragrances. Plants used for traditional medicine contain a wide range of substances that can be used to treat chronic as well as infectious diseases [4]. Phytochemically the plant has been investigated for cardenoloids, alkaloids, and saponins [5]. The plant was found to contain various triterpenes and steroidal compounds, and have been documented for antifertility [6], wound healing [7], antidiabetic [8], hepatoprotective [9], cardio-vascular effect [10], and antibacterial activity [11].

Pergularia daemia Linn. (Asclepiadaeceae) a foetid smelling lactioferous twinner found in the plains throughout the hotters parts of the India, ascending to an altitude of 1,000 m in the Himalayas [12]. Widely distributed in the old World tropics and sub-tropics from southern and tropical Africa through Arabia to Afghanistan, India and Sri Lanka [13]. Terpenoids, flavonoids, sterols and cardenolides are among the chemicals that have

been isolated from the leaves, stems, shoots, roots, seeds or fruit. Traditionally it has been used as an elmintic, laxative, antipyretic and expectorant, besides treatment of infantile diarrhoea, malarial intermittent fevers, toothaches and colds. Studies have shown hepatoprotective, antifertility, anti-diabetic, analgesic, antipyretic and anti-inflammatory properties of substances in its aerial parts [14].

Terminalia catappa Linn. (Combretaceae) is found in the warmer parts of India. It is also known as Indian almond, malabar almond, and tropical almond [15]. The various extracts of leaves and bark of the plant have been reported to be anticancer, possess antioxidant properties [16]. *Terminalia catappa* L. is a rich source of allagic acid, corilagin, gallic acid and many more unidentified flavonoids compounds [17].

Recently many researchers revealed pharmacological properties of the plant, among which are anti-inflammatory [18], anti-hepatitis [19], antibacterial [20] and many more. The present investigation is find out the interactions between the phytochemical compounds and selected targeted proteins through the molecular docking studies.

MATERIALS AND METHODS:

Collection of Plant Sample: The fully matured leaves of *Pergularia daemia* and *Terminalia catappa* (Red leaves) were collected in August – September 2012 from South Poigainallur Village in Nagapattinam district of Tamil Nadu, India and the plant was taxonomically identified by Dr. P. Jayaraman, plant anatomy research centre, West Tambaram, Chennai. The voucher specimen of *Pergularia daemia* (PARC/2013/211) and *Terminalia catappa* was (PARC/2014/2063).

Preparation of Extract: Matured leaves of *Pergularia daemia* and *Terminalia catappa* (Red leaves) were shade dried at room temperature and were powdered by using mechanical grinder. The hydro alcohol extracts of *Pergularia daemia* and *Terminalia catappa* were obtained by Soxhlet apparatus and extracting at 65 °C till discoloration. The extract was kept in air tight vials after complete evaporation and was stored in refrigerator till use.

Docking Studies:

Materials: To study the nature of interactions, binding mode of CYP2E1, Nrf_2 binding site in keap1, UDP Glucuronyl transferase and Glutathione-S-transferase, IL-6 with secondary metabolites of *Pergularia daemia* and *Terminalia catappa* L. docking was carried out with, autodock 4.2. autodock Tool was used for creating PDBQT files from traditional PDB files [21]. The sequence of CYP2E1 (Uniprot ID: P05181), UDP glucuronyl transferase (Uniprot ID: P22309), GSTP1 (Uniprot ID: P09211) and Nrf_2 binding site in keap1 (Uniprot ID: Q14145), IL-6 (Uniprot ID: P05231) were retrieved from uniprot database. The three dimensional structure of CYP2E1 (PDB ID: 3E6I), UDP glucuronyl transferase (prediction homology modeling), GSTP1 (PDB ID: 2A2R) and Nrf_2 binding site in keap1 (PDB ID: 4L7D), IL-6 (PDB ID: IALU) were downloaded from PDB database. The drug compound structures were drawn using ACD chemsketch and converted into PDB format using open Babel tool. The 3D structures of above targeted proteins were docked with various phytochemical compounds using autodock software. The docking results were analyzed using Discovery studio visualize tool.

The major chemical constituents present in the *Pergularia daemia* and *Terminalia catappa* L. Leaf extracts were drawn using chemsketch and optimized. Ligands were prepared in the autodock 4.2 for docking studies. The optimized ligands were docked into targeted proteins using "Ligand fit" model in autodock 4.2 [22]. The energy interaction between protein and ligand was calculated [23].

Auto Dock Calculation: Docking can be carried out by various methods. But, the most efficient method is lamarckian genetic algorithm. Autodock was run several times to get various docked conformations, and used to analyze the predicted docking energy. The binding sites for these molecules were selected based on the ligand-binding pocket of the templates [24]. Autodock tools provide various methods to analyze the results of docking simulations such as, conformational similarity, visualizing the binding site and its energy and other parameters like intermolecular energy and inhibition constant [25].

RESULTS AND DISCUSSION: In molecular docking studies, totally eight ligands were selected from GC-MS analysis of HAEPD and HAETC. The compounds like 4', 5, 7 trihydroxy isoflavone or genistein and pseudo baptigenin are present in both the plant extracts. The rest of the first three compounds (4H1Benzopyran one 7 hydroxy 2-phenyl, Dasycarpidan methanol acetate, mito-flaxone) from *Pergularia daemia* and second three compounds from *Terminalia catappa* (Apigenin 6-Cglucoside, 4H1Benzopyran 4one 5, 7 dihydroxy (3, 4, 5-tri methoxy phenyl, 4'Methoxy 5, 7-dihydroxy isoflavone) were taken. These compounds are selected for the docking studies. Auto docking 4.2 lab tool was used to perform the docking analysis of eight selective ligands with selected target proteins. Pseudo baptigenin, 4H1 benzopyran one 7-hydroxy 2-phenyl and 4' methoxy 5, 7-dihydroxy isoflavone, genistein were interacted CYP2E1 with least docking energy (-8.79, -8.2 and -8.16 Kcal /mol) with 1-3 hydrogen bonds. But the interaction energy of the other compounds with CYP2E1 ranges from -4.88 to -8.1 Kcal /mol with 1-2 hydrogen bonds **Table 1**, **Fig. 1**.

TABLE 1: CYP2E1 DOCKING WITH SELECTIVE LIGANDS

S. no.	Ligand name	Protein residue atom	Ligand atom	Hydrogen bond distance(A°)	No. of hydrogen bonds	Energy value (Kcal/mol)
1	Genistein	Thr307-OH	H	1.88	3	-8.16
		Thr307-OH	O	2.64		
		Gln358-O	H	1.91		
		Leu363-NH	O	2.84		
2	Pseudobapigenin	Thr304-OH	O	2.83	2	-8.79
		Gln358-O	H	1.91		
		Gln363-NH	H	2.92		
3	4H1Benzopyran one 7 hydroxy 2-phenyl	Leu363-NH	O	3.15	1	-8.2
		Gln358-O	H	2.12		
4	Dasycarpidan methanol acetate	Asp167-N	O	3.00	1	-4.88
5	Mitoflaxone	Arg100-NH	O	2.69	1	-8.1
6	Apigenin 6-C glucoside	Thr307-OH	H	2.98	2	-7.05
		Thr307-OH	H	2.07		
		Thr304-OH	O	2.51		
		Thr304-OH	O	3.09		
		Pro429-O	H	2.23		
7	4H1Benzopyran 4one5, 7-dihydroxy(3,4,5 tri methoxy phenyl	Thr307-OH	O	2.64	`1	-7.98
		Thr307-OH	H	1.87		
		Gln358-N	H	2.29		
8	4'Methoxy5,7-dihydroxy isoflavone	Leu363-NH	O	2.78	2	-8.2
		Gln358-O	H	1.82		
		Gln358-OH	H	2.35		

Many types of flavonoids act as chemopreventive compounds that inhibit the activity of different CYP2E1 isoenzymes. The hydroxyl derivatives of the flavones have been shown to differ in their inhibitory potency and isoenzymes selectivity [26]. Carty MC *et al.*, explained that the natural agents inhibiting CYP2E1, including diallyl sulphide (from garlic), phenyl ethyl isothiocyanate and sulforaphane (in cruciferous vegetables) and bergamottin (found in the essential oils of grape fruits and certain oranges) have been proposed as possible for minimizing the ethanol induced toxicity [27]. Jeong *et al.*, reported the YH439 is a noval synthetic compound that inhibit CYP2E1 that is being evaluated as a hepatoprotective agent [28]. In GSTP1 docking studies, the above phytochemicals, like the pseudo baptigenin, Apigenin 6-Cglucoside and 4H1Benzopyran one 7- hydroxy 2- phenyl, mitoflaxone were with least binding energy, and ranges from -7.1 to -7.88 Kcal/mol. These compounds exhibited 1-5 hydrogen bonds with the GSTP1 **Table 2**, **Fig. 2**.

Molecular docking studies of UDP Glucuronyl transferase with the phytochemicals present in HAEPD and HAETC. The compounds like genistein, pseudo baptigenin, 4H1Benzopyran one 7-hydroxy 2-phenyl, dasycarpidan methanol acetate, mitoflaxone and apigenin 6-cglucoside, 4h1benzopyran 4-one 5, 7-dihydroxy (3, 4, 5 tri methoxy phenyl, 4'Methoxy 5, 7- dihydroxy isoflavone (biochanin A) have shown better interaction energy with UDP glucuronyl transferase.

TABLE 2: GST DOCKING WITH SELECTIVE LIGANDS

S. no.	Ligand name	Protein residue atom	Ligand atom	Hydrogen bond distance(A°)	No. of hydrogen bonds	Energy value (Kcal/mol)
1	Genistein	Thr108-OH	O	2.90	2	-6.75
		Thr108-OH	H	2.31		
		Lys44-NH	O	2.83		
		Gly50-O	H	1.94		
		Trp38-NH	O	3.03		
2	Pseudobapigenin	Tyr108-OH	O	3.07	2	-7.88
		Trp38-NH	O	3.18		
		Lys44-NH	O	2.91		
		Gly50-O	H	1.78		
3	4H1Benzopyran one 7-hydroxy,2-phenyl	Ser65-NH	O	2.76	2	-7.25
		Tyr49-NH	O	3.06		
		Gln51-N	O	3.17		
		Gln51-O	H	2.25		
		Gln64-NE2	O	3.01		
4	Dasycarpidan methanol acetate	Tyr108-OH	O	2.94	1	-6.27
		Tyr7-OH	O	3.04		
		Asn204-NH	O	2.74		
5	Mitoflaxone	Gln51-NH	O	2.92	2	-7.1
		Trp38-NH	O	2.81		
		Lys44-NH	O	2.99		
6	Apigenin 6C glucoside	Lys44-NH	O	2.98	5	-7.34
		Trp38-NH	O	2.07		
		Gly50-O	H	2.51		
		Leu52-NH	O	3.09		
		Leu52 –O	H	2.23		
		Arg100-NH	O	2.54		
		Try108-OH	O	2.91		
7	4H1Benzopyran 4-one-5, 7-dihydroxy (3, 4, 5-trimethoxyphenyl	Ser65-OH	H	1.76	`2	-5.95
		Ser65-OH	O	2.54		
		Gln64-N	O	3.12		
		Gln64-NH	O	3.16		
		Pro53-O	H	2.36		
8	4’Methoxy-5, 7-dihydroxy isoflavone	Tyr108-OH	O	3.04	2	-6.55
		Trp38-NH	O	2.96		
		Lys44-NH	O	2.98		
		Gly50-O	H	2.02		

TABLE 3: UGT DOCKING WITH SELECTIVE LIGANDS

S. no.	Ligand name	Protein residue atom	Ligand atom	Hydrogen bond distance(A°)	No. of hydrogen bonds	Energy value (Kcal/mol)
1	Genistein	Lys328-O	H	2.28	2	-5.77
		Lys328-NH	O	2.92		
		Ser143-O	H	2.12		
2	Pseudobapigenin	Ser445-O	H	1.79	2	-7.49
		Ser445-NH	O	2.73		
		Tyr379-OH	O	2.79		
3	4H1Benzopyran one 7-hydroxy, 2-phenyl	His132-O	H	1.77	3	-7.91
		His132-NH	O	3.19		
		Ser128-OH	O	2.71		
4	Dasycarpidan methanol acetate	Glu291-NH	O	2.98	1	-6.17
5	Mitoflaxone	Asn384-NH	O	3.07	4	-6.33
		Asn384-O	H	2.17		
		Gln288-NH	O	2.75		
		Lys437-NH	O	3.01		
6	Apigenin 6C glucoside	His132-NH	O	1.75	3	-5.56
		Glu291-OH	H	2.23		
		Arg367-NH	O	3.09		
		Arg367-NH	O	2.95		
		Glu289- OH	H	1.95		
7	4H1Benzopyran 4-one 5, 7-dihydroxy (3, 4, 5-tri methoxy phenyl	Tyr379-O	H	1.81	`1	-6.33
		Gly21-O	H	2.01		
		Gly21-NH	O	3.18		
		Ser445- NH	O	2.85		
8	4’Methoxy-5, 7-dihydroxy isoflavone	Phe145-NH	O	3.18	2	-6.47
		Glu135-OH	H	1.95		
		Asn133-NH	O	2.85		

TABLE 4: Nrf_2 BINDING SITE IN KEAP 1 DOCKING WITH SELECTIVE LIGANDS

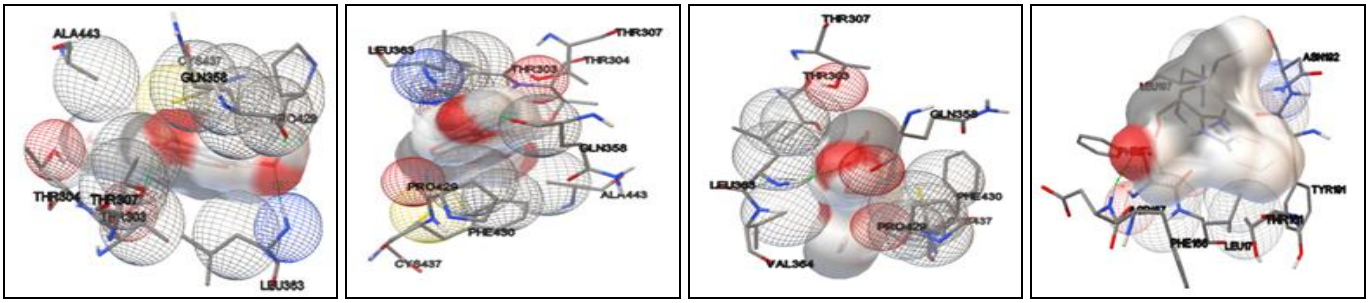
S. no.	Ligand name	Protein residue atom	Ligand atom	Hydrogen bond distance(A°)	No. of hydrogen bonds	Energy value (Kcal/mol)
1	Genistein	Val606-O	H	2.42	4	-8.18
		Val606-NH	O	3.06		
		Val418-O	H	2.19		
		Val418-NH	O	2.99		
		Val 467-O	H	2.35		
		Val 467-NH	O	2.69		
2	Pseudonapigenin	Val 467-O	H	2.23	3	-8.75
		Val 467-NH	O	3.01		
		Val606-NH	O	3.06		
		Ileu559-NH	O	2.93		
3	4H1Benzopyran one 7-hydroxy, 2-phenyl	Val606-NH	O	2.68	3	-7.41
		Gly367-NH	O	3.20		
		Val465-O	H	1.90		
		Val465-NH	O	2.83		
4	Dasycarpidan methanol acetate	Thr560-OH	O	2.55	2	-7.63
		Val561-NH	O	2.71		
5	Mitoflaxone	Gln530-OH	O		5	-6.76
		Ser555-OH	O	2.92		
		Ser508-OH	O	2.66		
		Arg483-NH	O	3.19		
		Arg483-NH	O	2.69		
6	Apigenin 6C glucoside	Val418-O	H	1.96	5	-8.78
		Thr560-OH	O	2.95		
		Ile559-O	H	2.05		
		Ile559-NH	O	3.12		
		Gly367-O	H	1.93		
		Gly367-O	H	1.92		
7	4H1Benzopyran 4-one 5, 7-dihydroxy (3, 4, 5-tri methoxy phenyl	Val604-O	H	1.91	`3	-8.23
		Val369-NH	O	3.06		
		Thr560-OH	O	2.65		
8	4'Methoxy-5, 7-dihydroxy isoflavone	Leu559-O	H	3.04	3	-7.97
		Leu559-NH	O	2.96		
		Ileu557-O	H	2.98		
		Val465-NH	O	2.02		

TABLE 5: IL6 DOCKING WITH SELECTIVE LIGANDS

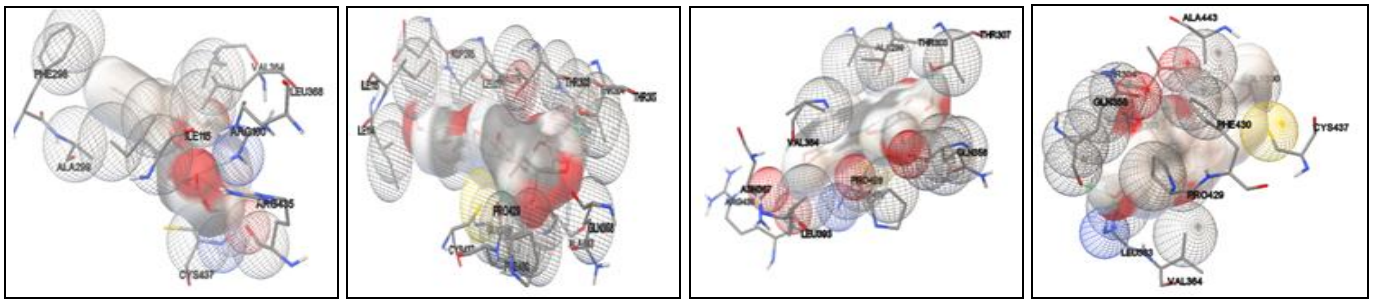
S. no.	Ligand name	Protein residue atom	Ligand atom	Hydrogen bond distance(A°)	No. of hydrogen bonds	Energy value (Kcal/mol)
1	Genistein	Gln175-NH	O	3.01	3	-6.14
		Arg179-NH	O	2.91		
		Arg182-NH	O	3.13		
		Arg30-NH	O	3.01		
		Asp34-O	H	2.06		
2	PseudoBapigenin	Arg179-NH				
		Arg182-NH	O	2.83	4	-7.13
		Arg179-NH	O	3.09		
		Asp34-OH	H	1.98		
3	4H1Benzopyran one 7-hydroxy, 2-phenyl	Arg30-NH	O	3.02	1	-6.18
4	Dasycarpidan methanol acetate	Asp140-NH	O	2.97	1	-5.13
5	Mitoflaxone	Agr30-NH	O	2.93	2	-6.73
		Arg30-NH	O	2.98		
6	Apigenin 6C glucoside	Asp71-OH	H	1.92	4	-4.92
		Lys86-NH	O	2.48		
		Leu62-O	H	1.97		
		Leu62-O	H	1.74		
		Leu62-O	H	2.48		
		Leu62-NH	O	2.86		
7	4H1Benzopyran 4-one 5, 7-dihydroxy (3, 4, 5-tri methoxy phenyl	Lys66-NH	O	2.85	`3	-5.88
		Lys66-O	H	1.82		
		Lys86-NH	O	2.72		
8	4'Methoxy-5, 7-dihydroxy isoflavone	Lys27-NH	O	2.63	1	-5.85
		Arg182-O	H	2.02		

The 4H1Benzopyran one 7-hydroxy 2-phenyl shown least interaction energy (-7.91 Kcal/mol, 3-hydrogen bonds) was followed by pseudo baptigenin (-7.49 Kcal/mol, 2 hydrogen bonds) against UDP glucuronyl transferase **Table 3, Fig. 3**. Artali *et al.*, demonstrated that the 89% of HGSTP1 docking sites for four green tea catechins occurred at enzyme subunits interface [29].

The binding sites for catechins included Gln52, Pro54, Asn67, Glu97, Asp94 and also residues that overlap with G site (Tyr8, Phen9, Arg14, Trp39, Gln66, Ser67, Glu98) or the H-site (Tyr104, Tyr108, Gly208). Other residues for catechin binding were (Thr68, Arg71, Arg75, Asp91, Asp95 and Asp99) located at the subunit - subunit interface.

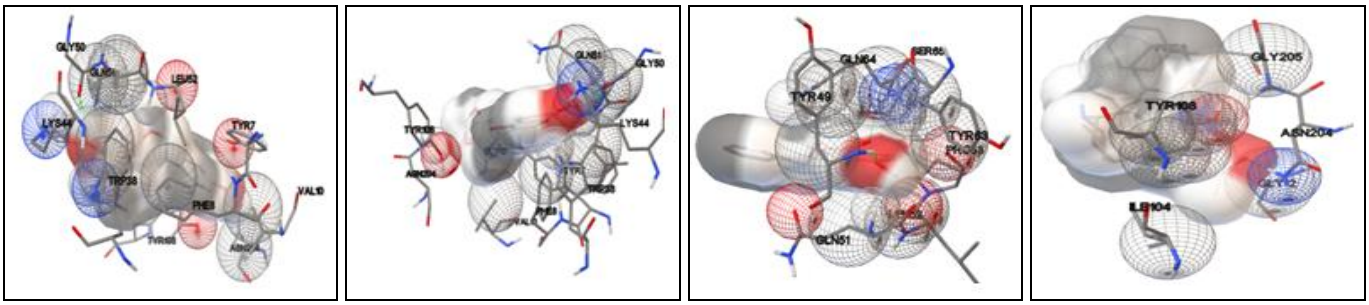


GENISTEIN | **PSEUDOBAPIGENIN** | **4H1BENZOPYRAN ONE 7-HYDROXY 2 PHENYL** | **DASYCARPIDAN METHANOL ACETATE**



MITOFLAXONE | **APIGENIN 6 C GLUCOSIDE** | **4H1BENZOPYRAN 4ONE 5, 7-DIHYDROXY (3, 4, 5 TRI METHOXY PHENYL** | **4'METHOXY5, 7-DIHYDRO ISOFLAVONE**

FIG. 1: INTERACTION OF LIGANDS WITH CYP2E1



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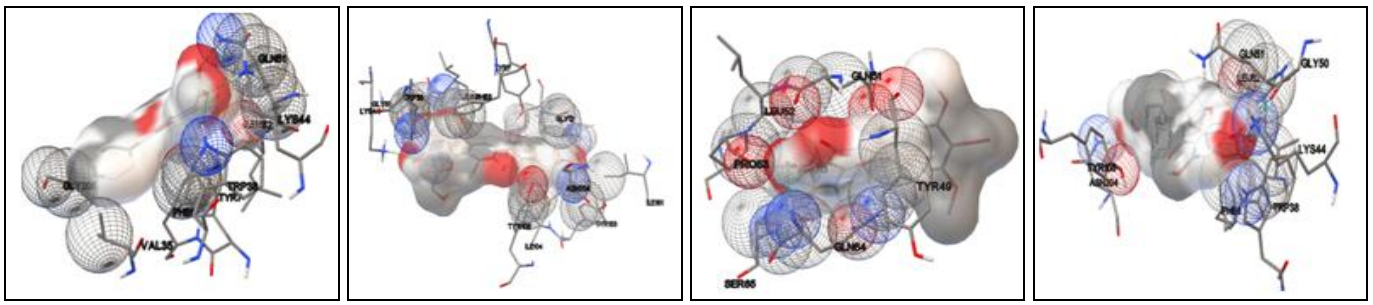

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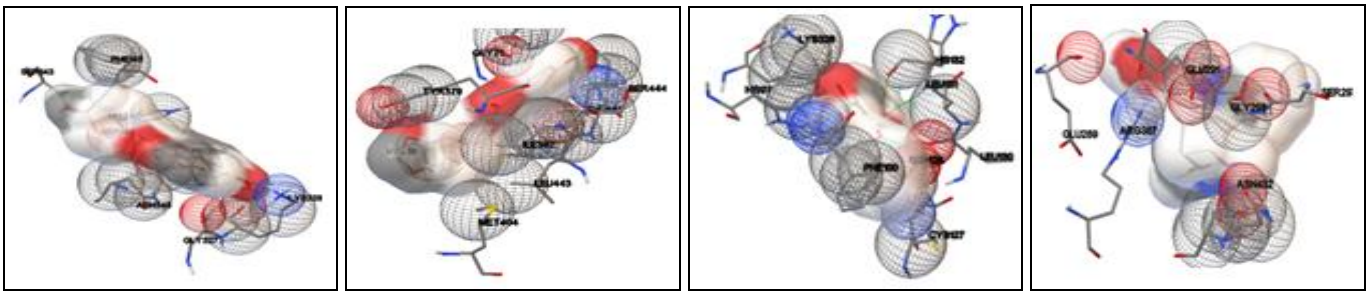
FIG. 2: INTERACTION OF LIGANDS WITH GSTP1



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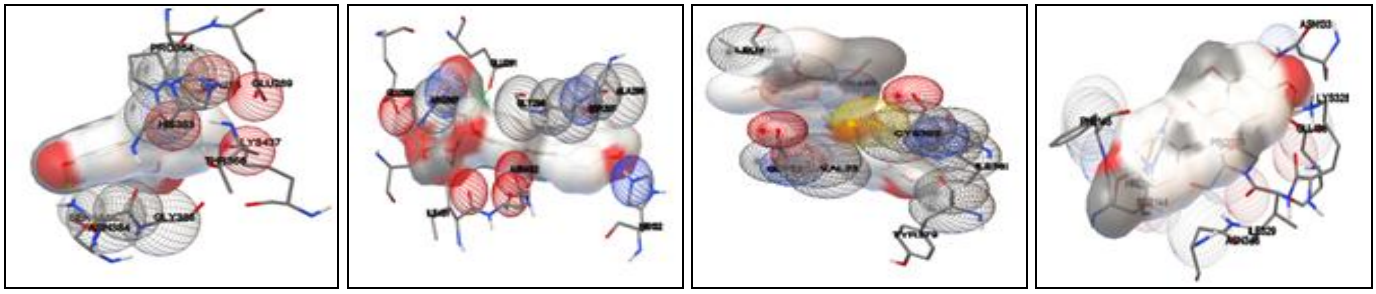
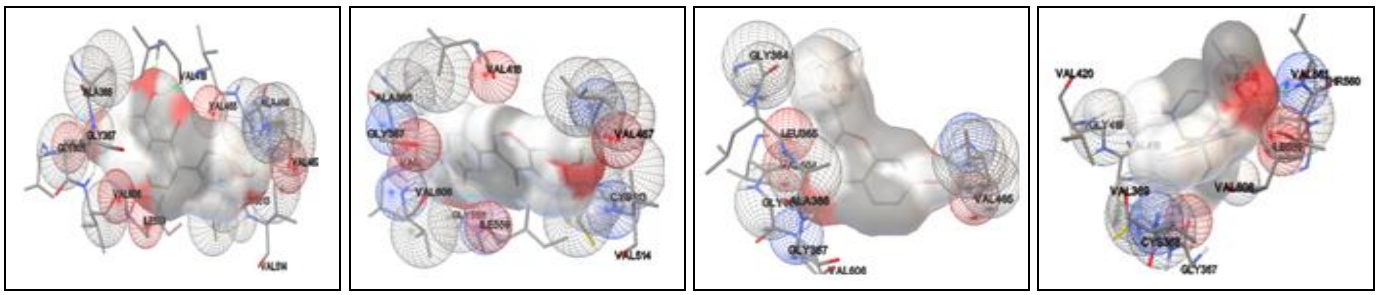


MITOFLAXONE | **APIGENIN 6 C GLUCOSIDE** | **4H1BENZOPYRAN 4ONE 5, 7-DIHYDROXY (3, 4, 5 TRI METHOXY PHENYL** | **4'METHOXY5, 7-DIHYDRO ISOFLAVONE**

FIG. 3: INTERACTION OF LIGANDS WITH UGT1A1



GENISTEIN | **PSEUDOBAPIGENIN** | **4H1BENZOPYRAN ONE 7-HYDROXY 2 PHENYL** | **DASYCARPIDAN METHANOL ACETATE**

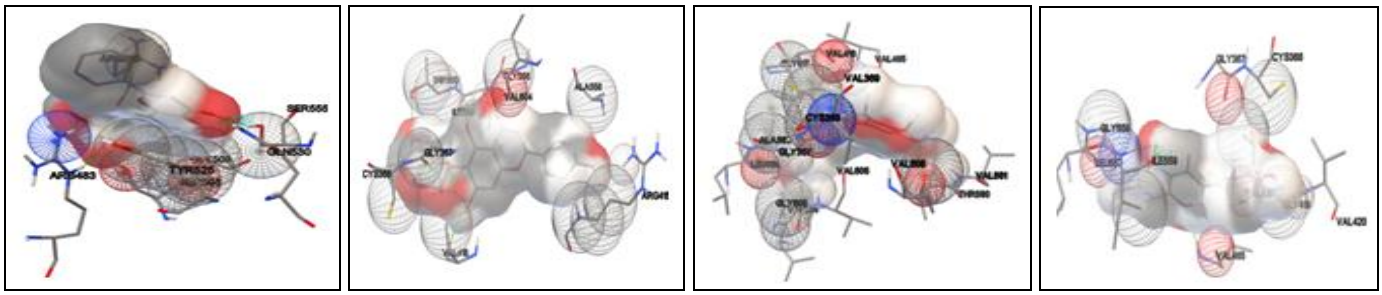


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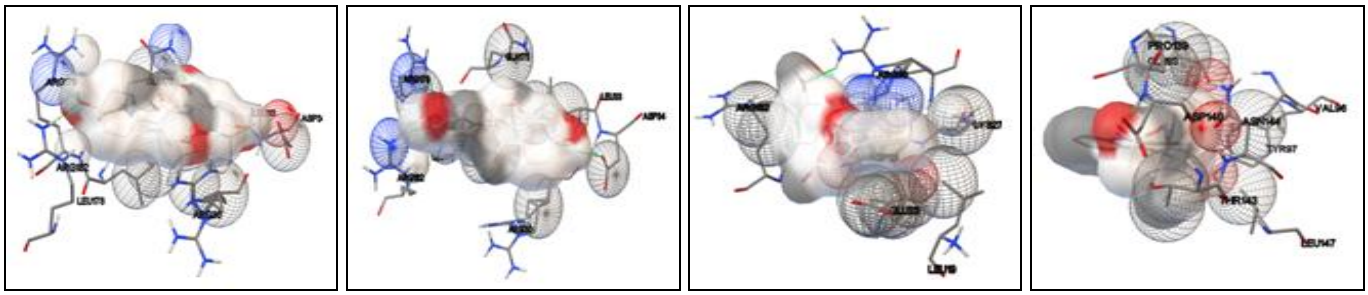
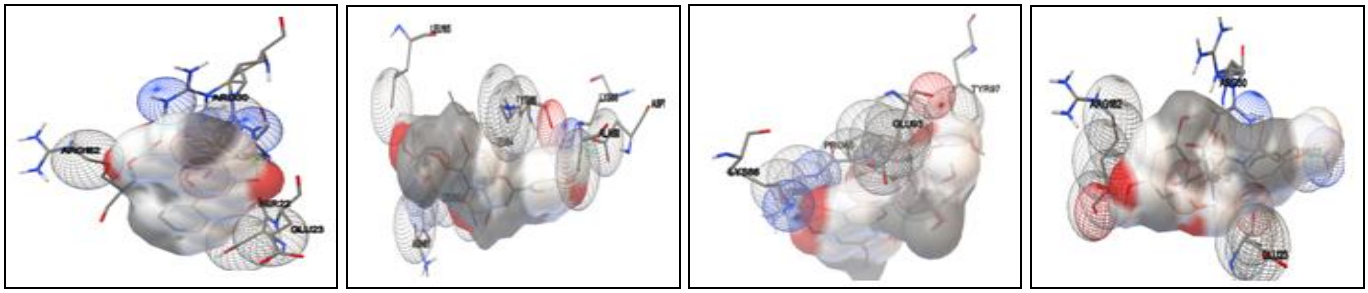
FIG. 4: INTERACTION OF LIGANDS WITH NRF2 BINDING SITE IN KEAP1



GENISTEIN | **PSEUDOBAPIGENIN** | **4H1BENZOPYRAN ONE 7-HYDROXY 2 PHENYL** | **DASYCARPIDAN METHANOL ACETATE**



MITOFLAXONE | **APIGENIN 6 C GLUCOSIDE** | **4H1BENZOPYRAN 4ONE 5, 7-DIHYDROXY (3, 4, 5 TRI METHOXY PHENYL** | **4'METHOXY5, 7-DIHYDRO ISOFLAVONE**

FIG. 5: INTERACTION OF LIGANDS WITH IL-6

Curcumin has been shown to induce GSTP1 expression with involvement of transcription factor Nrf_2 in human hepatic cells [30]. It also able to induce the protection and activate Nrf_2 dependent protective response in cell lines or animal models exposed to oxidative condition [31].

Keep 1 protein docked with the eight ligands from HAEPD and HAETC. All these phytochemicals bind with keap1 protein and the interaction energy ranges from -6.76 to -8.78 Kcal/moles. The stronger interaction was observed with apigenin 6C glucoside, pseudobaptigenin, mitoflaxone and 4H1benzopyran 4one 5, 7-dihydroxy (3, 4, 5 tri-methoxy phenyl, with 3 to 5 hydrogen bonds **Table 4, Fig. 4**.

The least interaction energy were observed with apigenin 6C glucoside, pseudobaptigenin, mito-flaxone and 4h1benzopyran 4one 5, 7-dihydroxy (3, 4, 5 trimethoxy phenyl and genistein with keap1 protein. The interaction energy were -8.78, -8.75, -8.23 and -8.18 Kcal/mol with 3 to 5 hydrogen bonds.

Many of these antioxidant cytoprotective enzymes are controlled by the same three components of transcription pathway: the antioxidant response elements (ARE), the nuclear factor erythroids 2-related factor (Nrf_2) and the Kelch like ECH associated protein 1 (Keap1).

Yoon *et al.,* (2008) reported sulforaphane is present in cruciferous vegetables. This compound have antioxidant, anti inflammatory and it is used to reduced the renal dysfunction. These effects were mediate by the induction of phase II enzymes by decreasing the keap1 protein level and increasing Nrf_2 nuclear translocation [32].

Silvian and colleagues identified two compounds (Benzene sulfonyl - pyrimidone and N-Phenyl benzene sulphonamide) as Keap1 –Nrf_2 PPI inhibitors. The N-Phenyl benzene sulphonamide bind with central cavity of Keap1 kelch domain and form the electrostatic, hydrophobic interaction with the domain. Three serine (Ser 508, 555, 602) and arginine (Arg 415,483) in the keap1 kelch domain form hydrogen bonds with n-phenyl benzene sulphonamide [33].

Table 5 and **Fig. 5**, explained the interaction between IL-6 and phytochemicals from HAEPD and HAETC. The least interaction energy value (-7.13 Kcal/mole) and maximum number of hydrogen bonds (4 bonds) was found in pseudo bapigenin and followed by mitoflaxone (-6.73 Kcal/mol), 4H1Benzopyran one 7- hydroxy 2 phenyl (-6.18 Kcal/mol). Remaining compounds interact with IL-6 and the interaction energy range from -4.92 to -6.14 Kcal/mol with 1 to 4 hydrogen bonds.

Interleukin-6 is a pleiotropic cytokine showing essential roles in immunity, hematopoisis and inflammation [34, 35, 36, 37]. Arginine (Arg) at the 179th position of IL-6 plays an important role targeting this particular site in IL-6 will impair its normal function. Five natural compounds (heptadecanoic acid, 2-(2-(2 carboxybenzyl) amino)-2-oxo ethyl) benzoic acid, 2-(2-(2 carboxy benzyl) acetamido benzoic acid and (S) methyl 2-(3-(7 methoxy -4-methyl -2-oxo -2H- chromen -6yl) propanamido) -3- phenyl propanoate, 2- (2- (3- (isopropyl carbamoyl) phenyl) amino)- 2- oxoethyl) benzoic acid) were used in *in-silico* docking studies. These compounds interacted with the active site amino acids (Arg 179) of IL-6.

These compounds may crucial in blocking considerably elevated IL-6 in the serum of rheumatoid arthritis patients [38]. Vkronique fontaine *et al.,* (1993) reported that the 171 -179 amino acids deletion of human interleukin -6 (IL-6) leads biological inactivation of IL-6. The Arg 179th position of IL-6 play an important role in ligand interaction [39].

Naurally occurring compounds like curcumin, lycopene, sulforaphane, oganosulfur compounds in garlic etc have been reported as potent activators of Nrf2 by inhibiting KEAP1, which has been linked to their chemopreventive and chemotherapeutic effects. The binding cavity of KEAP 1 is divided into 5 subpockets as P1, P2, P3, P4 and P5, where two subpocket, P1 and P2, play significant role in strong binding interactions and contribute to total binding free energy. The P1, formed by residues Ser508, Phe478, Ile461, Arg483, Arg415, and Gly462, is highly positively charged and the electrostatic interactions with the Arg483 and Arg415 are significant for binding [40, 41, 42].

Flavonoids can exert protective effects by selectively inhibiting or stimulating key proteins in cell signalling cascades and modulate the activity of enzymes, including phase 1 and phase 2 biotransformation enzymes. Although flavonoids have attracted considerable attention as inducer of enzymes involved in phase 2 biotransformation mediated by the EpRE [43]. The phytochemicals from GC-MS studies were used in molecular docking, that showed good binding with targeted proteins. These compounds gives satisfactory binding with CYP2E1, Nrf2 binding site in keap1 and IL-6, phase II enzymes with least interaction energy and greater number of hydrogen bonds.

These phytochemicals that blocks CYP2E1, Nrf_2 binding site in keap1, IL-6 and activates Nrf_2 pathway, Phase II enzymes (detoxification enzymes). Based on the docking results, the above phytochemicals may possess the effectiveness against hepatotoxicity.

CONCLUSION: Naturally occurring compounds like curcumin, lycopene, sulforaphane, oganosulfur compounds in garlic etc have been reported as potent activators of Nrf2 by inhibiting KEAP1, which has been linked to their chemopreventive and chemotherapeutic effects. The binding cavity of KEAP 1 is divided into 5 subpockets as P1, P2, P3, P4 and P5, where two subpocket, P1 and P2, play significant role in strong binding interactions and contribute to total binding free energy. The P1, formed by residues Ser508, Phe478, Ile461, Arg483, Arg415, and Gly462, is highly positively charged and the electrostatic interactions with the Arg483 and Arg415 are significant for binding [40-42].

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