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Evaluation of Phytochemicals Constituents of *Gyrocarpus asiaticus* Willd. and *Lactuca runcinata* DC for Antioxidant Activity by Molecular Docking Study

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In this study, based on the molecular docking study, the antioxidant activity of phytochemicals constituents of hydroalcoholic extract of *Gyrocarpus asiaticus* Willd. and *Lactuca runcinata* DC were evaluated. For molecular docking study, ligand generation of phytochemicals constituents of *Lactuca runcinata* DC and *Gyrocarpus asiaticus* Willd. were performed by visualizing software Biovia Discovery Studio. The docking study of two proteins *viz*. NADPH oxidase (PDB ID 2CDU) and human carbonyl reductase–I (PDB ID 3BHI) with the identified phytochemicals constituents was done by Auto Dock Vina. Depending on the docking score, the best three compounds were selected from each plant. For physico-chemical properties prediction and toxicity of these compounds were predicted by the Swiss ADME and Orisis properties explorer.

Keywords: *Lactuca runcinata* DC, *Gyrocarpus asiaticus* Willd., Molecular docking, Toxicity, Swiss ADME.

INTRODUCTION

In recent years, the exploration of natural products as potential sources of therapeutic agents has gained significant thrust in the field of medicinal chemistry and drug discovery [1]. The remarkable diversity of secondary metabolites produced by plants has made them a rich repository of bioactive compounds with various pharmacological properties [2]. Among these properties, the antioxidant activity of phytochemicals has drawn considerable attention due to its potential in preventing or mitigating oxidative stress-related diseases [3,4].

Gyrocarpus asiaticus Willd., commonly known as helicopter tree or spinning jenny, is an indigenous plant found in various parts of Asia and Africa. It has a long history of use in traditional medicine for its reported anti-inflammatory and antioxidant properties [5]. *Lactuca runcinata* DC, on the other hand, belongs to the Asteraceae family and is commonly known as wild lettuce. It has been used traditionally for its analgesic and sedative properties and is believed to possess bioactive compounds with antioxidant potential [6].

Oxidative stress, characterized by an imbalance between the production of reactive oxygen species (ROS) and the body's ability to detoxify them, plays a pivotal role in the development of various diseases, including cancer, neurodegenerative disorders and cardiovascular diseases [7]. The human body has an intricate defense system comprising endogenous antioxidants and enzymes to counteract the harmful effects of ROS [8]. However, when this defense system is overwhelmed, exogenous antioxidants from dietary sources or medicinal plants can provide crucial support in combating oxidative stress [9].

The evaluation of antioxidant activity often involves the identification and assessment of specific phytochemicals present in plant extracts. Gas Chromatography-mass spectrometry (GC-MS) is a powerful analytical technique used for the separation and identification of various compounds present in complex mixtures [10]. In this study, the main phytochemical constituents of the hydroalcoholic extracts of *Gyrocarpus asiaticus* Willd. and *Lactuca runcinata* DC isolated were considered for the docking studies. These constituents serve as potential candidates for the evaluation of antioxidant activity.

Molecular docking is a computational technique widely employed in drug discovery and the study of molecular interactions. It allows us to predict the binding affinity and interactions between small molecules (ligands) and target proteins (receptors) [11]. In present study, two biologically significant proteins, NADPH oxidase (PDB ID-2CDU) and human carbonyl reductase -I (PDB ID-3BHI) were selected, both of which have been implicated in oxidative stress-related pathways [12,13]. By employing Auto Dock Vina, a popular molecular docking software, we aimed to explore the binding affinities of identified phytochemical constituents from *Gyrocarpus asiaticus* Willd. and *Lactuca runcinata* DC with these target proteins.

The selection of the best compounds from each plant was based on docking scores, which indicate the strength of the ligand-receptor interactions [14]. Three compounds with the highest docking scores were chosen for further investigation. Additionally, to assess the safety and pharmacokinetic properties of these selected compounds, Swiss ADME and Orisis Properties Explorer were utilized for the predictions regarding the physico-chemical properties and potential toxicity [15]. This study represents an integrated approach to evaluate the antioxidant potential of phytochemical constituents from *Gyrocarpus asiaticus* Willd. and *Lactuca runcinata* DC. The combination of analytical techniques such as GC-MS and computational tools like Auto Dock Vina, Swiss ADME and Orisis Properties Explorer provides valuable insights into the bioactive compounds from these plants and their potential as therapeutic agents in combating oxidative stress-related diseases. The results of this study may contribute to the development of natural antioxidant-based therapies, thereby advancing the field of medicinal chemistry and promoting the utilization of traditional medicinal plants in modern medicine.

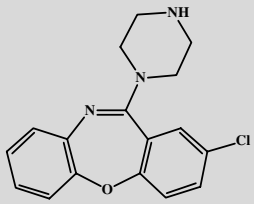
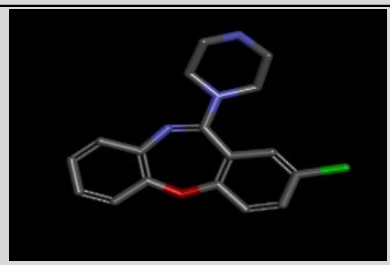
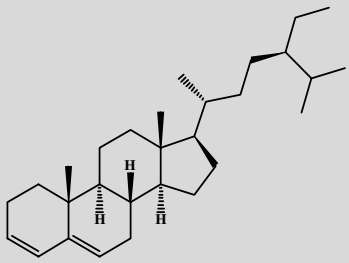
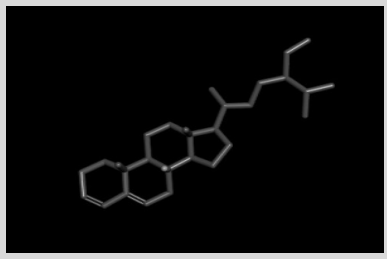
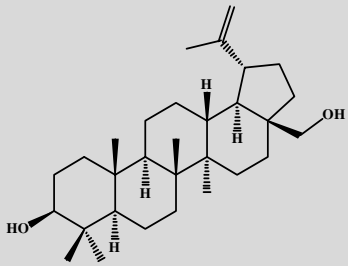
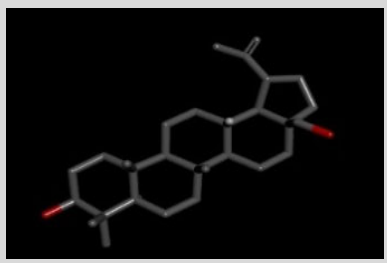
EXPERIMENTAL

Chemdraw Professional 16.0 software was used to draw the 2D structure of phytochemicals constituents. Auto Dock 4.2 software was used to generate ligands and receptors for molecular docking. Auto Dock Vina software was used for the molecular docking score generation, whereas Biovia Discovery Studio Software was used for visualization the receptor and phytochemicals constituent's interaction.

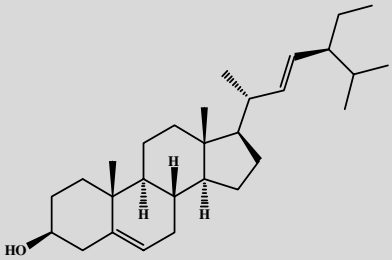
Ligand generation of phytochemicals constituents: For molecular docking study, ligand generation of phytochemicals constituents of *L. runcinata* DC and *G. asiaticus* Willd. were performed by visualizing software Biovia Discovery Studio. From the 2D structure of all phytochemicals constituents of *L. runcinata* DC and *G. asiaticus* Willd. converted to pdbqt format for molecular docking. The 2D structures of the phytochemicals isolated from *L. runcinata* DC and *G. asiaticus* Willd. are shown in Table-1.

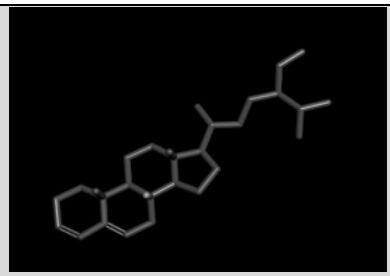
Receptors and binding sites: The 3D structure of NADPH oxidase (PBD ID: 2CDU) and human carbonyl reductase–I

TABLE-1
LIGAND GENERATION OF 2D STRUCTURE OF PHYTOCHEMICALS CONSTITUENT'S STRUCTURE OF *Gyrocarpus asiaticus* Willd. AND *Lactuca runcinata* DC.

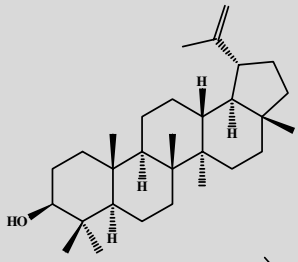
Compound	Chemical structure	2D Structure
***Gyrocarpus asiaticus* Willd.**		
Amoxapine		
Stigmasta-3,5-diene		
Betulin		

Stigmasterol

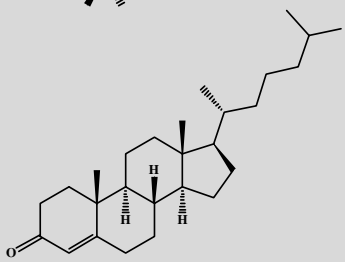


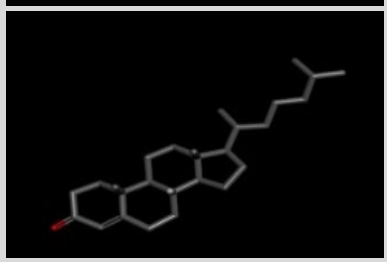


Lupeol

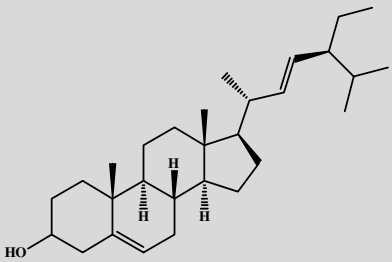


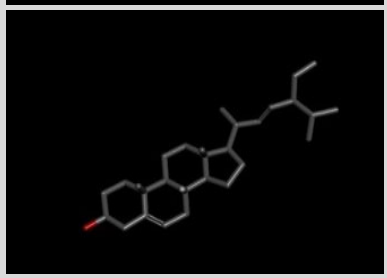
Cholest-4-en-3-one



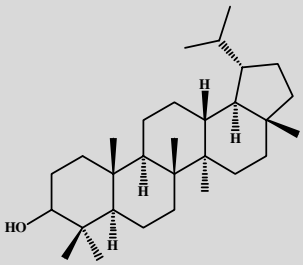


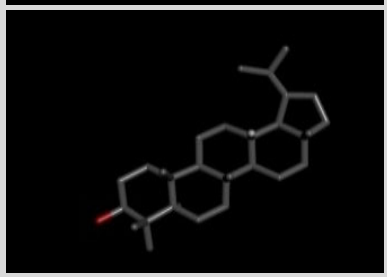
Stigmasta-5,22-dien-3-ol



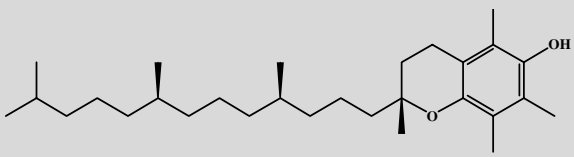


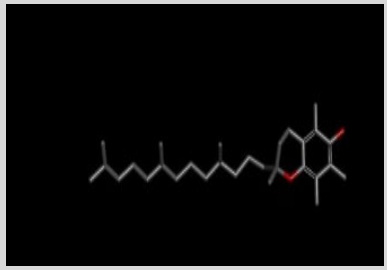
Lupan-3-ol



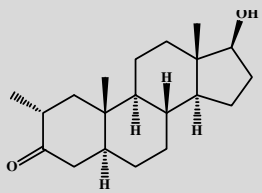


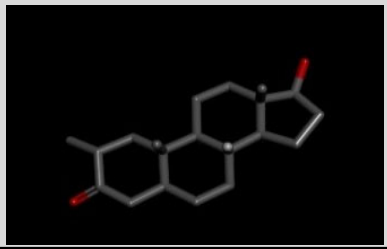
Vitamin E





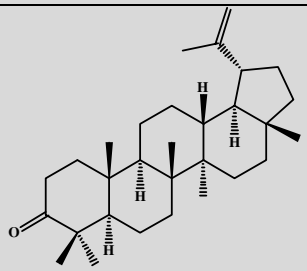
Drostanolone

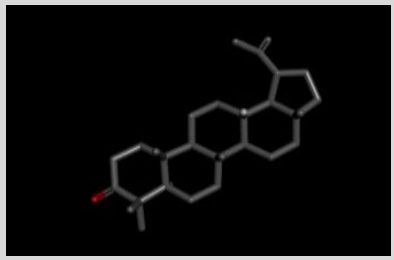




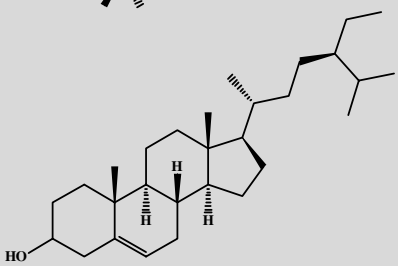
***Lactuca runcinata* DC.**

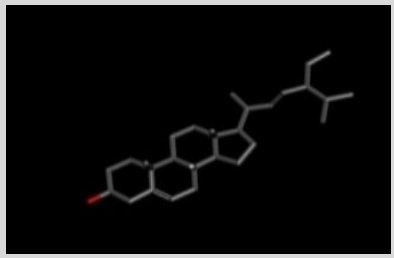
Lup-20(29)-en-3-one



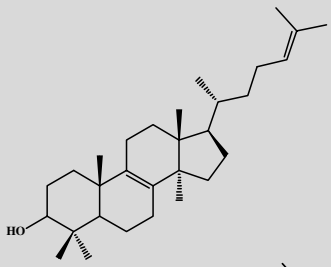


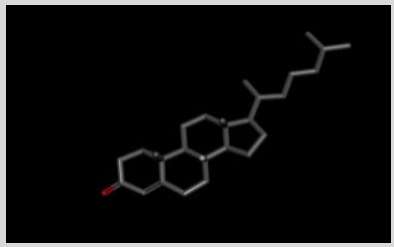
Stigmast-5-en-3-ol



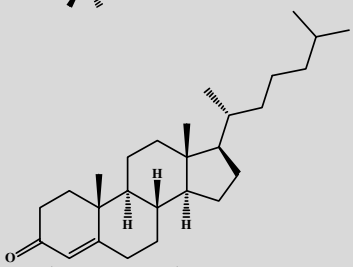


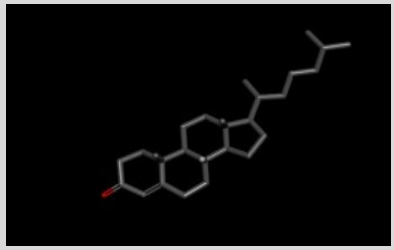
Lanosterol



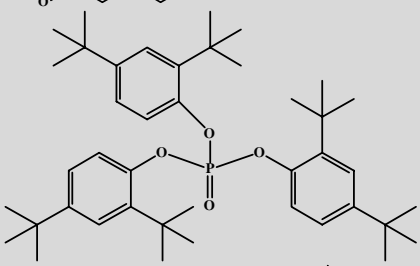


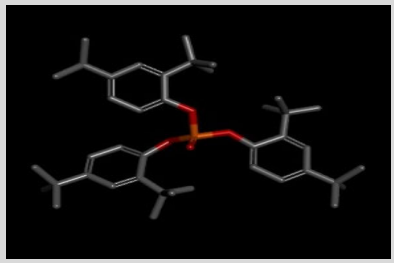
Cholest-4-en-3-one



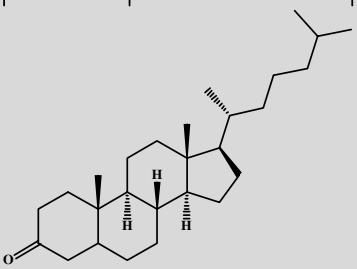


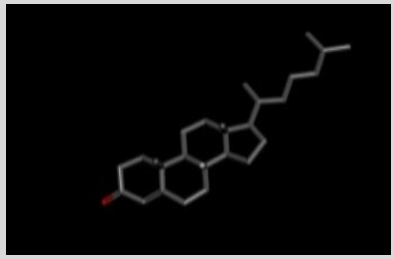
Tris(2,4-di-*tert*-butylphenyl) phosphate



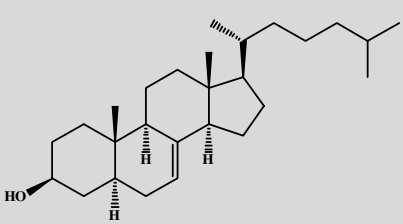


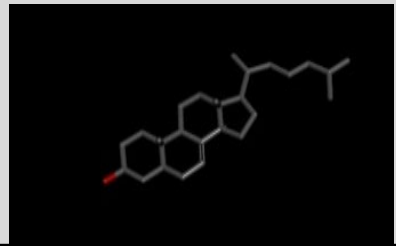
Cholestan-3-one

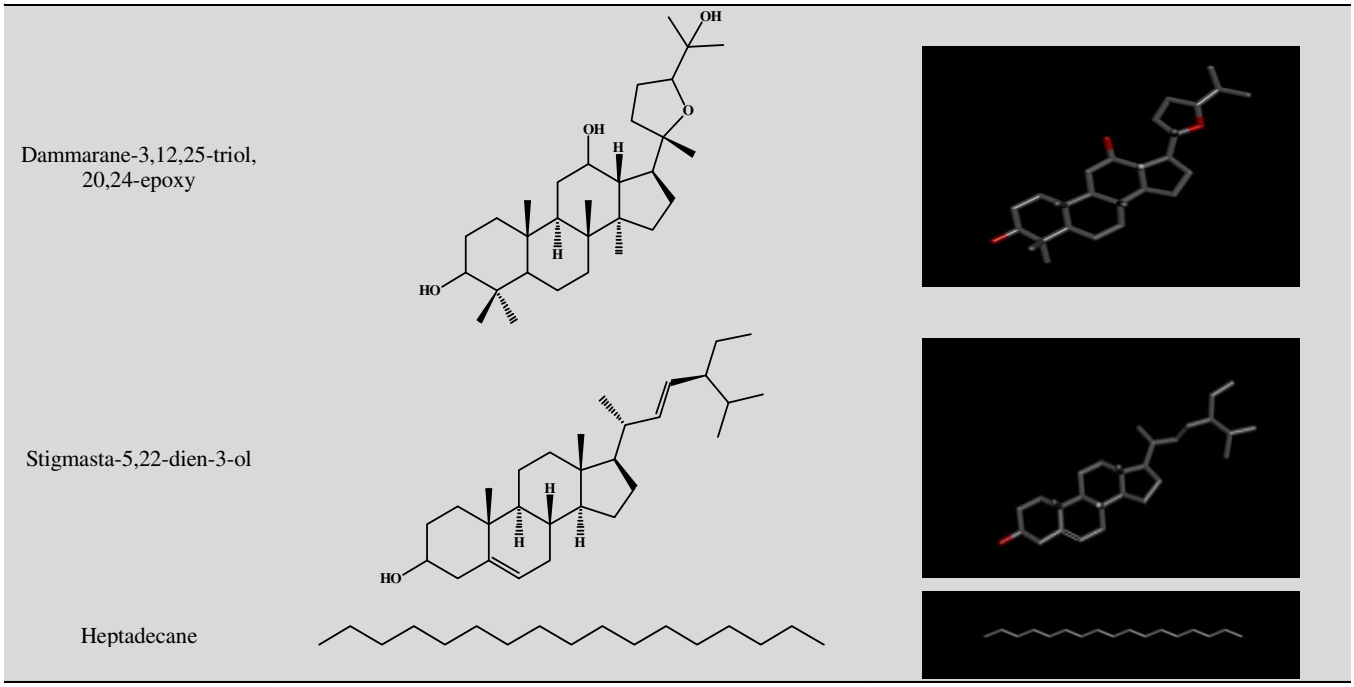




Lathosterol







(PDB ID: 3BHI) was retrieved from the website www.rcsb.org. The 3D structure of these two proteins were prepared by removing water molecule from structure and separate the attached ligand from proteins and then converted the structure format with the help of Auto Dock 4.2 (Fig. 1). Molecular docking with these two proteins with the ten identified phytochemicals constitution of *L. runcinata* DC and *G. asiaticus* Willd. by Auto Dock Vina. Docking score with binding affinity with all compounds generated by Auto Dock Vina and depending on the docking score best three compounds were selected. Binding affinity with different amino acids of proteins with all these phytochemical's 2D image were retrieved by the using of visualizing software Biovia Discovery Studio 2020 [16].

Physico-chemical properties and toxicity prediction: Various interactions with different amino acids with plant phytoconstituents by various bonds can be seen by 2D images generated by visualizing software Biovia Discovery studio. Depending on the docking score and interaction three best compounds were selected from the 10 compounds used for molecular docking. The physico-chemical properties of best three compounds like lipophilicity, hydrogen bond donor capacity, molecular weight, hydrogen bond acceptor (Pfizer rule of 5) was predicted by the Swiss ADME for its drug likeness properties. Any toxicity effects like tumorigenic or mutagenic or having any irritant effects or having any effects on reproductive system of these compounds was predicted by Osiris Property Explorer [17].

RESULTS AND DISCUSSION

From the GC-MS analysis of *G. asiaticus* Willd., the phytochemicals constituents like amoxapine, stigmasta-3,5-diene, betulin, stigmasterol, lupeol, cholest-4-en-3-one, stigmasta-5,22-dien-3-ol, lupan-3-ol, vitamin E, drostanolone were identified by depending upon highest peak area and peak height.

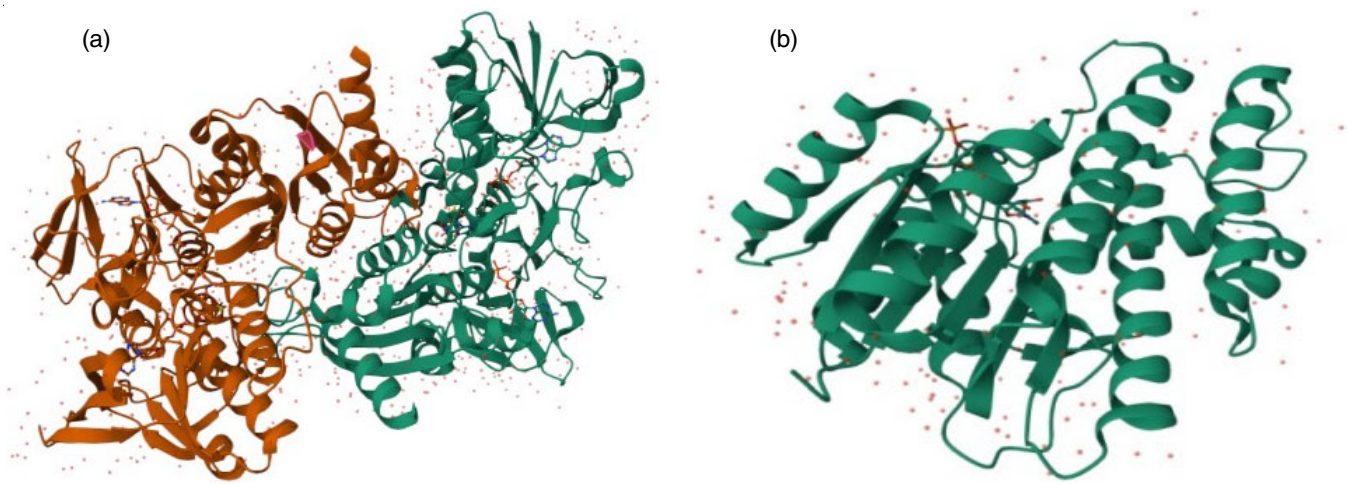


Fig. 1. 3D structure of (a) NAD(P)H oxidase (PDB ID-2CDU) and (b) human carbonyl reductase I (PDB ID-3BHI)

Based on the docking score or binding affinity, amoxipine, stigmasta-5,22-dien-3-ol and drostanolone show the highest binding affinity with these proteins. Amoxapine shows -9.5KJ/mol binding affinity with NADPH oxidase protein and -9.6 KJ/mol binding affinity with human carboxylase reductase–I protein. Stigmasta-5,22-dien-3-ol shows -9.8 KJ/mol binding affinity with NADPH oxidase protein and -8.9 KJ/mol binding affinity with human carboxylase reductase–I protein and drostanolone shows -9.8 KJ/mol binding affinity with NADPH oxidase protein and -8.7 KJ/mol binding affinity with human carboxylase reductase–I (Table-2).

Based on the molecular docking results, amoxapine (Fig. 2), stigmasta-5,22-dien-3-ol (Fig. 3) and drostanolone (Fig. 4) show the highest binding affinity towards proteins. The hydro-alcoholic extract of *G. asiaticus* Willd. shows good antioxidant activity [18], so considering that these three molecules *viz.* amoxapine, stigmasta-5,22-dien-3-ol and drostanolone could be responsible for antioxidant activity. To check the drug likeness properties of these three compounds the physico-chemical properties prediction was performed by Swiss ADME web tool. Results (Table-3) show that the amoxapine having drug likeness properties and follows the Lipinski's rule of 5 with no violation, stigmasta-5,22-dien-3-ol having drug likeness properties and follows the Lipinski's rule of 5 with one violation (lipophilicity-5.01) and drostanolone also follow Lipinski's rule of five with no violation. Permeability prediction was also done by Swiss ADME (boiled egg study), where the results showed that amoxapine and drostanolone having good permeability properties, can cross blood brain barrier and having high gastrointestinal absorption, whereas stigmasta-5,22-dien-3-ol has low gastrointestinal absorption and limited brain permeability (Table-4). Toxicity prediction conducted by Orisis properties shows that all the three compounds has no mutagenic, tumorigenic, irritant effects and has high risk effects on reproductive system.

Based on the docking score of *Lactuca runcinata* DC generated by Auto Dock Vina, cholest-4-en-3-one (Fig. 5), cholestan-3-one (Fig. 6) and stigmasta-5,22-dien-3-ol (Fig. 7) shows the highest binding affinity with the studied proteins (Table-2). The physico-chemical properties and toxicity study were performed by Swiss ADME and Orisis properties explorer and all three compounds shows follow of Lipinski's rule of 5

TABLE-2
BINDING AFFINITY OF IDENTIFIED COMPOUNDS OF *Gyrocarpus asiaticus* Willd AND *Lactuca runcinata* DC WITH RECEPTORS

Ligand	*Gyrocarpus asiaticus* Willd		Ligand	*Lactuca runcinata* DC	
	NAD(P)H oxidase (KJ/mol)	Human carbonyl reductase-I (KJ/mol)		NAD(P)H oxidase (KJ/mol)	Human carbonyl reductase-I (KJ/mol)
Amoxapine	-9.5	-9.6	Lup-20(29)-en-3-one	-8.7	-9.2
Stigmasta-3,5-diene	-9.1	-7.2	Stigmast-5-en-3-ol	-9.2	-9.6
Betulin	-8.2	-8.0	Lanosterol	-8.8	-8.6
Stigmasterol	-7.7	-8.5	Cholest-4-en-3-one	-9.8	-8.3
Lupeol	-8.4	-7.7	*Tris*(2,4-di-*tert*-butylphenyl) phosphate	-9.1	-8.9
Cholest-4-en-3-one	-8.6	-7.6	Cholestan-3-one	-9.5	-8.2
Stigmasta-5,22-dien-3-ol	-9.8	-8.9	Lathosterol	-8.8	-7.0
Lupan-3-ol	-8.2	-6.7	Lupan-3-ol	-8.2	-7.5
Vitamin E	-7.6	-7.2	Stigmasta-5,22-dien-3-ol	-9.8	-8.8
Drostanolone	-9.8	-8.7	Heptadecane	-8.8	-7.3

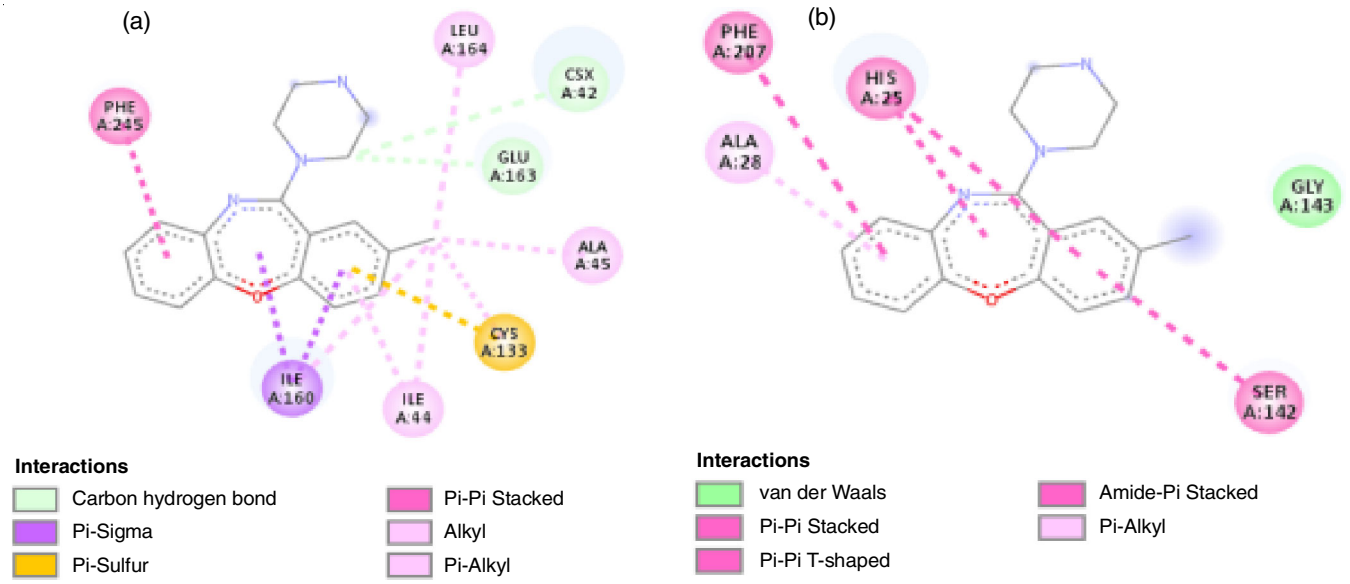


Fig. 2. Amoxapine interaction with (a) NAD(P)H oxidase and (b) human carbonyl reductase I

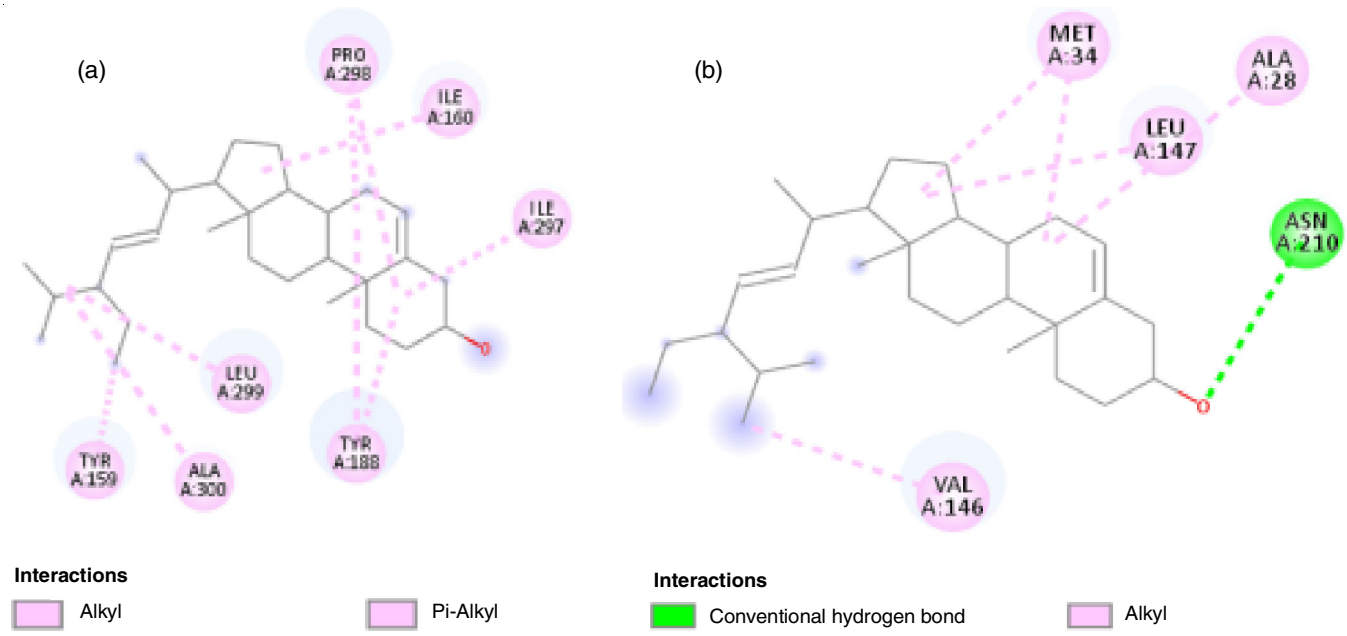


Fig. 3. Stigmasta-5,22-dien-3-ol interaction with (a) NAD(P)H oxidase and (b) human carbonyl reductase I

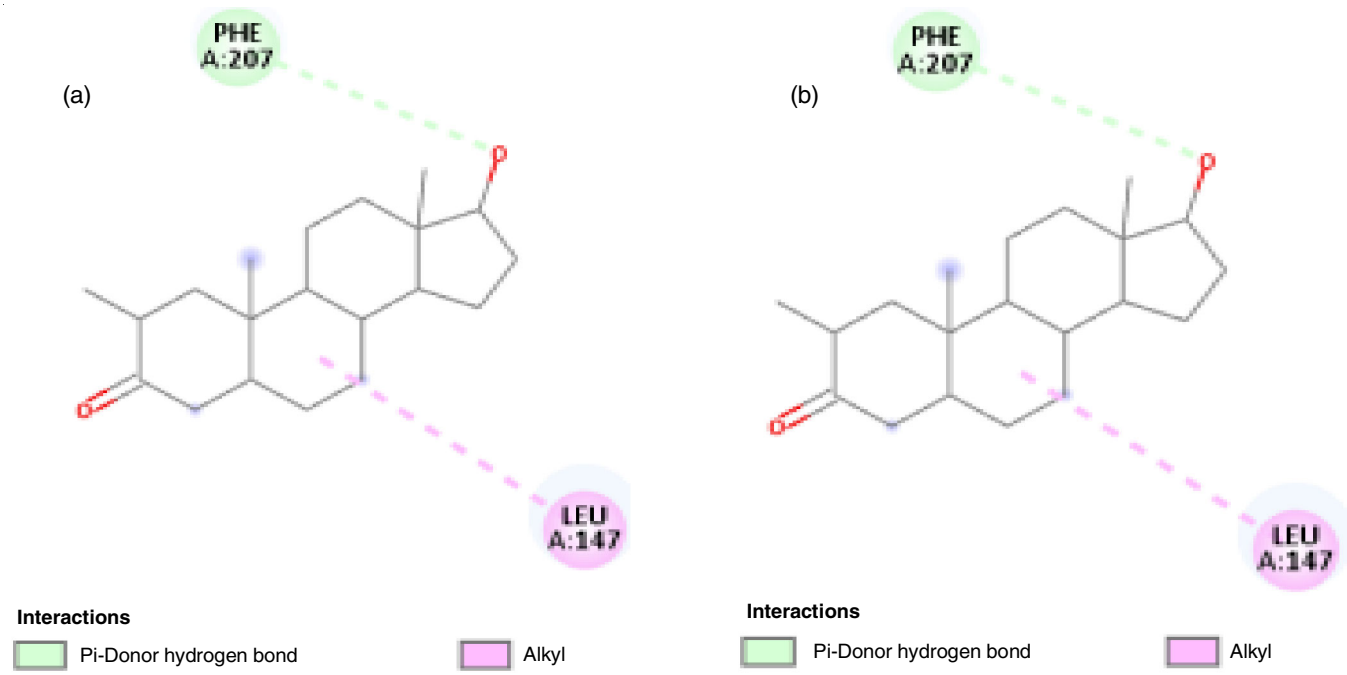


Fig. 4. Drostanolone interaction with (a) NAD(P)H oxidase and (b) human carbonyl reductase I

TABLE-3
PHYSICO-CHEMICAL PROPERTIES PREDICTION OF AMOXAPINE, STIGMASTA-5,22-DIEN-3-OL, DROSTANOLONE ISOLATED FROM *Gyrocarpus asiaticus* Willd BY SWISS ADME

Molecule	m.f.	m.w. (g/mol)	Lipophilicity (logP)	Hydrogen bond donor	Hydrogen bond acceptor
Amoxapine	$C_{17}H_{16}CLN_{30}$	313.78	3.04	1	3
Stigmasta-5,22-dien-3-ol	$C_{29}H_{48}0$	412.69	5.01	1	1
Drostanolone	$C_{20}H_{32}O_2$	304.47	3.09	1	2

with no violation (Table-5). Toxicity prediction study indicates that all the three compounds shows no mutagenic and irritant effects, however, cholest-4-en-3-one and cholestan-3-one have high risk of reproductive effect. Similarly, both compounds have low GI absorption and limited brain permeability whereas stigmasta-5,22-dien-3-ol has no mutagenic, tumorigenic,

TABLE-4
TOXICITY PREDICTION OF AMOXAPINE, STIGMASTA-5,22-DIEN-3-OL, DROSTANOLONE ISOLATED FROM *Gyrocarpus asiaticus* Willd USING ORISIS PROPERTIES EXPLORER

Compound	Mutagenic	Tumorigenic	Irritant	Reproductive effective	Permeability (Boiled Egg)
Amoxapine	No effect	No effect	No effect	High risk effects	The yellow region- can cross blood brain barrier and having high gastrointestinal absorption.
Stigmasta-5,22-dien-3-ol	No effect	No effect	No effect	No effect	Grey region - low absorption and limited brain permeation
Drostanolone	No effect	No effect	No effect	High risk effects	The yellow region- can cross blood brain barrier and having high gastrointestinal absorption.

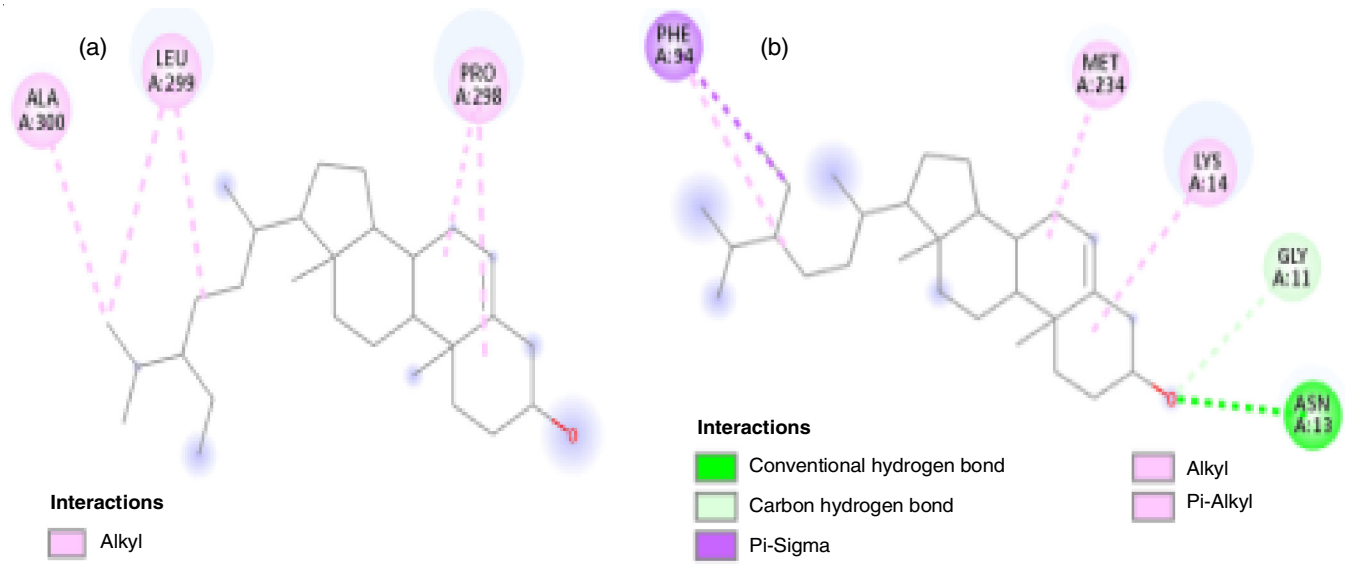


Fig. 5. Cholest-4-en-3-one interaction with (a) NAD(P)H oxidase and (b) human carbonyl reductase I

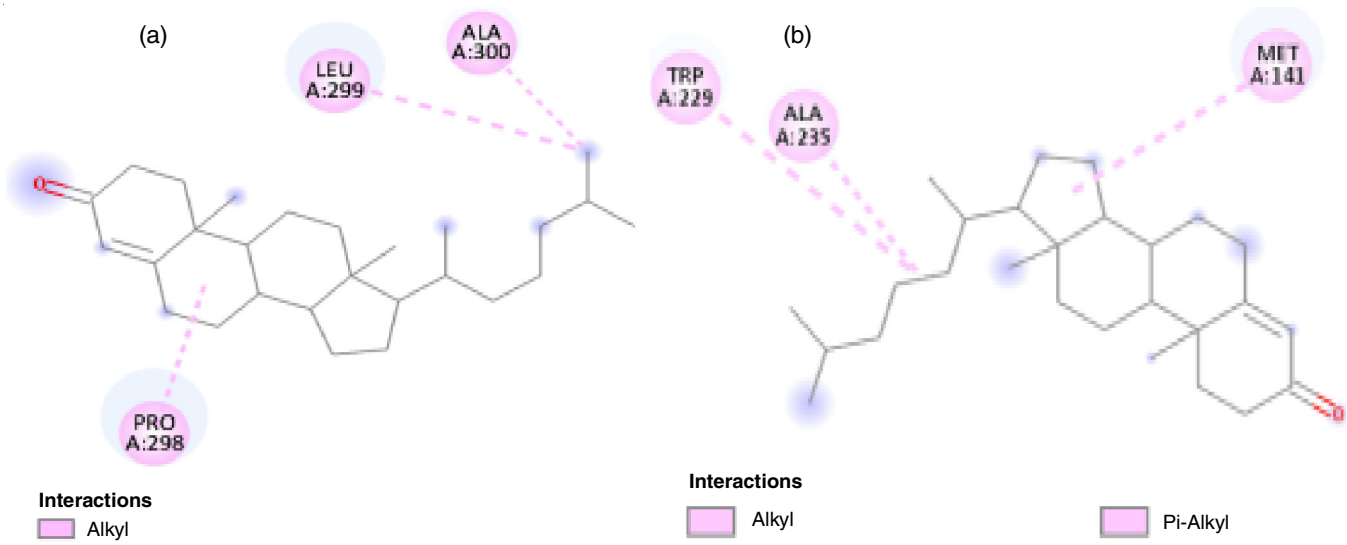


Fig. 6. Cholestan-3-onel interaction with (a) NAD(P)H oxidase and (b) human carbonyl reductase I

TABLE-5
PHYSICO-CHEMICAL PROPERTIES PREDICTION OF CHOLEST-4-EN-3-ONE, STIGMASTA-5,22-DIEN-3-OL, CHOLESTAN-3-ONE ISOLATED FROM *Lactuca runcinata* DC BY SWISS ADME

Molecule	m.f.	m.w. (g/mol)	Lipophilicity (logP)	Hydrogen bond donor	Hydrogen bond acceptor
Cholest-4-en-3-one	$C_{27}H_{44}O$	384.64	4.71	0	1
Cholestan-3-one	$C_{27}H_{44}O$	384.64	4.71	0	1
Stigmasta-5,22-dien-3-ol	$C_{29}H_{48}0$	412.69	5.01	1	1

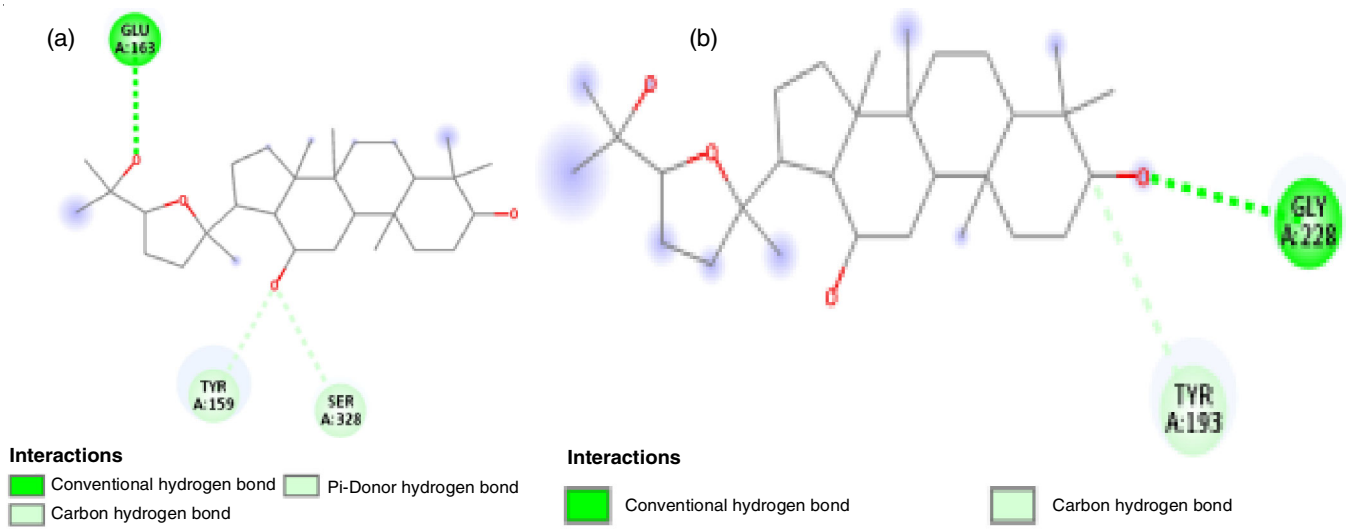


Fig. 7. Stigmasta-5,22-dien-3-ol interaction with (a) NAD(P)H oxidase and (b) human carbonyl reductase I

TABLE-6
TOXICITY PREDICTION OF CHOLEST-4-EN-3-ONE, STIGMASTA-5,22-DIEN-3-OL, CHOLESTAN-3-ONE ISOLATED FROM *Lactuca runcinata* DC USING ORISIS PROPERTIES EXPLORER

Compound	Mutagenic	Tumorigenic	Irritant	Reproductive effective	Permeability (Boiled Egg)
Cholest-4-en-3-one	No effect	Medium risk	No effect	High risk	Grey region - low absorption and limited brain permeation
Cholestan-3-one	No effect	Medium risk	No effect	High risk	Grey region - low absorption and limited brain permeation
Stigmasta-5,22-dien-3-ol	No effect	No effect	No effect	No effect	Grey region - low absorption and limited brain permeation

irritant and reproductive effects with limited brain permeability, low absorption (Table-6).

Conclusion

The purpose of the *in silico* study is to assess the antioxidant activity of phytochemical ingredients by molecular docking analysis. This work aims to provide evidence supporting the *in vitro* antioxidant activity of the hydroalcoholic extract from *Gyrocarpus asiaticus* Willd. and *Lactuca runcinata* DC. Based on the high docking scores, cholest-4-en-3-one, chole-stan-3-one and stigmasta-5,22-dien-3-ol, the main phytoconstituents of *L. runcinata* DC, whereas amoxapine, stigmasta-5,22-dien-3-ol and drostanolone the main constitutents of *G. asiaticus* Willd. shows the interaction with different amino acid of NAD(P)H oxidase and human carbonyl reductase-I with different bonds like van der Waals bond, alkyl bond, pi-bond, conventional hydrogen bond. Inhibition of these protein with different interaction by the phytochemicals constituents of *G. asiaticus* Willd. and *L. runcinata* DC resulting inhibition of oxidative stress and responsible for antioxidant activity. The physico-chemical properties of all three compounds of *Lactuca runcinata* DC follow the Lipinski's rule of five and in the toxicity prediction study cholest-4-en-3-one and cholestan-3-one shows no mutagenic and irritant effects but have high risk effects on reproductive system. The main phytoconstitutents of *G. asiaticus* Willd. *viz.* amoxapine, drostanolone and stigmasta-5,22-dien-3-ol also show good binding affinity with various amino acids of NAD(P)H oxidase and human carbonyl reduc-tase-I and has no mutagenic, tumorigenic, irritant effects, but high risk effects on reproductive system.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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