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Review Article

Mechanistic Insights an Anthelmintic Potential of *Cleome viscose* Seeds: "Molecular Docking"

Rizwan Ahmad[1*], Jitender K Malik[1]

[1]Institutes of Pharmacy, P.K. University, Shivpuri (M.P.)-India

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***Corresponding author:** Rizwan Ahmad
Institutes of Pharmacy, P.K. University, Shivpuri (M.P.)-India

Abstract

Herbal remedies used traditionally to cure different types of human disease. The research in herbal drugs, to discover single compound used a lead for developing new therapeutically active products. *Cleome viscosa* Linn. (wild or dog mustard), belongs to family(Capparaceae). *Cleome viscosa* well known plant for their antimicrobial, anti-diarrheal, hepatoprotective, analgesic and anti-fibrolytic potential. In living beings, infection caused by helminths (helminthiasis) is a severe problem to health that results in hardship and stunted growth. In the developing world, helminthiasis (in human intestine) is the most common infectious disease. The seed contained salicylic acid and Lupeol. This study has been carried out to evaluate anthelmintic potential of *Cleome viscose* seed by molecular docking via drug-tubulin interaction. The molecular docking result revealed that salicylic acid and Lupeol showed encouraging docking score. The docking score found to be -1.98 and -3.82 kcal mol^{-1} respectively.

Keywords: *Cleome viscosa*, salicylic acid and Lupeol, docking score, molecular docking & β-tubulin.

INTRODUCTION

The therapeutic effectiveness of many indigenous plants, for various diseases has been described by traditional herbal medicinal practitioners. Natural products are the basis of synthetic and traditional herbal medicine [1, 2]. Helminthiasis, an infection brought on by helminths that causes difficulty and stunted growth in living things, is a serious health issue. The most prevalent infectious disease in the poor world is helminthiasis, which affects the human intestine. Helminths are now resistant to commercially available medications, and they are very expensive. Worldwide, parasitic illnesses continue to be a significant barrier to the production of live livestock. A nematode parasite called *Haemonchus contorn* feeds on the blood of tiny ruminants, which results in anaemia, loss of appetite, sluggish growth, and eventually death of the host animal. A key barrier to the global production of healthy sheep and goats is H. contortus, a highly pathogenic parasite of small ruminants [3]. Researchers are striving to screen for solutions in order to overcome the issues via screen the anthelmintic agents from natural plant sources. In existing era, focus is laid to investigate and identify the plants with anthelmintic potential. Currently chemical substance used in the treatment of helminthiasis is expensive, beneficial against only one group of organisms and lose their efficacy within 20 years [4]. *Cleome viscosa* Linn (Capparidaceae), usually known as "wild or dog mustard".

Cleome viscosa

The whole system and its parts (leaves, seeds, and roots) are often used in medical and folklore systems. In traditional drug systems, plants are reported to have an effective effect as in traditional systems of medicine the plant is reported to possess beneficial

effects as an anthelmintic, antiseptic, carminative, antiscorbutic, sudorific, febrifuge, and cardiac stimulant [5, 6]. *Cleome viscose* showed various pharmacological potential like Analgesic, antiemetic, antidiarrhoeal, Heptoprotective, antifibrotic and antitumor [7-11]. As per literature survey salicylic acid and Lupeol was present in ethyl acetate extract [12].Molecular docking of anthelmintic drug with β-tubulin to study the activity by drug-tubulin interaction is already proven by Grace basumatary *et al.*, 2020 [13] because inhibition of β -tubulin of the helminths can severely affect their vital cellular functions such as mitosis, motility, and transport. Therefore, in order to rationalize the anthelmintic activity of the active compounds present in ethyl acetate seed extract of *Cleome viscose* and understand their possible interactions, molecular docking simulation of the compounds have been carried out against β -tubulin.

Experimental Work

Docking Study of Lupeol with β Tubulin

Molecular Docking Studies

Ligand Preparation

2D Structure of ligand lupeol was drawn by using ChemDraw. The two-dimensional structures of ligands were converted into 3-D structures with optimized 3D geometry by using Chem3D software. The optimized structure was saved in PDB format for AutoDock compatibility [14].

Preparation of the Grid File

The regions of interest used by Auto dock were defined by considering grid area by making a grid box around the active sites. Grid box plays a central role in process of docking as it is made to cover all the amino acids present in active sites necessary for binding other than those present in receptor. Grid box has 3 thumbwheel widgets which let us change the number of points in the x, y and z dimensions. The spacing between grid points can be adjusted with another thumbwheel, the value in the study taken is 0.392 Å and No. of points considered are 40, 40 and 40 points in the x, y, and z dimensions are 16.741, 11.602 and 27.751 as x, y, z centers [15].

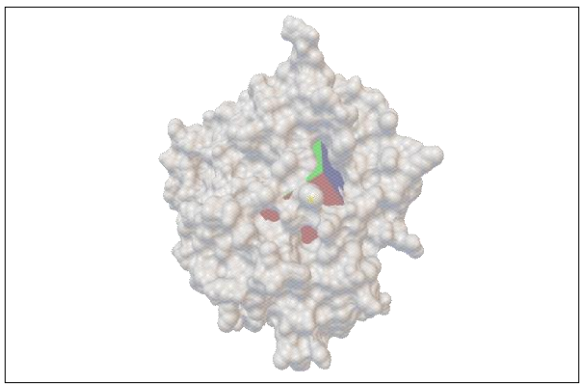

Figure 1: Grid box covering all active sites in receptor

Preparation of the Docking File

All the calculations were carried out by using Autodock 4.2 as docking tool. The visualization and other programs necessary for docking studies were performed out by means of Pymol, Chimera, DS visualizer, MMP Plus [16].

Macromolecular Structure

The crystal structure of the β-tubulin receptor consisting of receptor associated with bound mebendazole ligand is downloaded from the Protein Data Bank portal. All the primary information regarding receptor and structure (7odn.pdb) registered in the Protein data bank was used. The bound ligand mebendazole (V95) was found within the receptor [17].

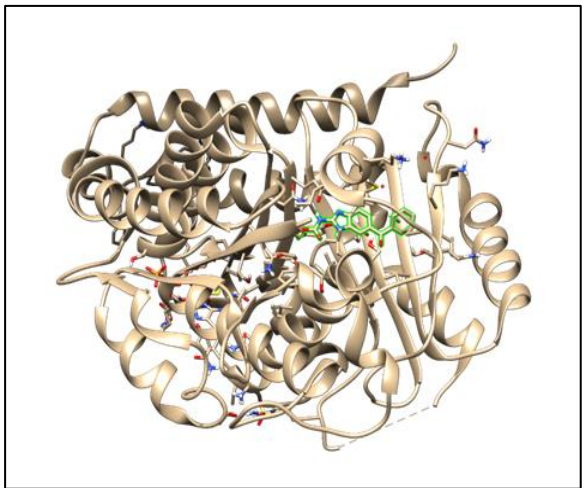

Figure 2: Crystal structure of β tubulin receptor with bound ligand V95 (PDB ID-7odn)

Processing of Protein

The downloaded receptor protein is having two chains A and B, out of which chain B has been selected for the experimental purpose. The bound ligand V95 was separated from the macromolecular complex by using software Chimera [18].

Molecular Docking Simulation Studies

Docking of ligand lupeol against beta tubulin receptor was performed by Autodock. All the bonds of lupeol ligand were kept flexible, while no residues in receptor were made flexible [19].

Toxicity & ADME-T Studies

The pharmacokinetics of ligand molecule was studied by online program OSIRIS, for prediction of presence of any toxic group as well as presence of any toxic group and ADME-T properties [20].

Salicylic Acid with Beta Tubulin

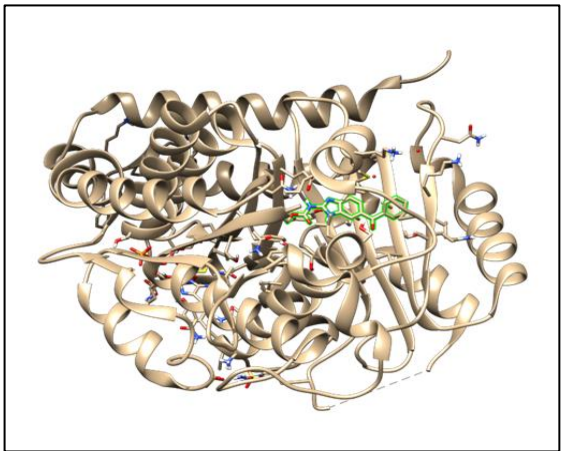

Figure 3: Crystal structure of β tubulin receptor with bound ligand V95 (PDB ID-7odn)

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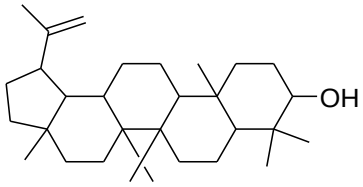
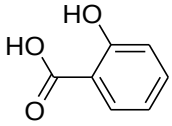
Molecular Docking Simulation Studies

Docking of ligand salicylic acid against β tubulin receptor was performed by Auto dock. All the bonds of salicylic acid ligand were kept flexible, while no residues in receptor were made flexible [22].

Toxicity & ADME-T Studies

The pharmacokinetics of ligand molecule was studied by online program OSIRIS, for prediction of presence of any toxic group as well as presence of any toxic group and ADME-T properties [23].

Table 1: Result of docking of against β- tubulin receptor

S. No	CompoundName	Structure	B.E.	H-Bond	Residual Interaction	
					Pi-Interaction	van der Waals
1	Lupeol		-1.98	Nil	Lys254, Ala316, Ala354, Val318, Ile378, Leu248, Leu255, Met259, Lys352	Asn258, Ala250, Thr317, Val238, Ser241, Val315, Val351
2	Salicylic acid		-3.82	Gly237	Ala316, Ala354, Val318, Thr317	Asn258, Ala250, Thr317, Val238, Ser241, Leu248,

Interactions

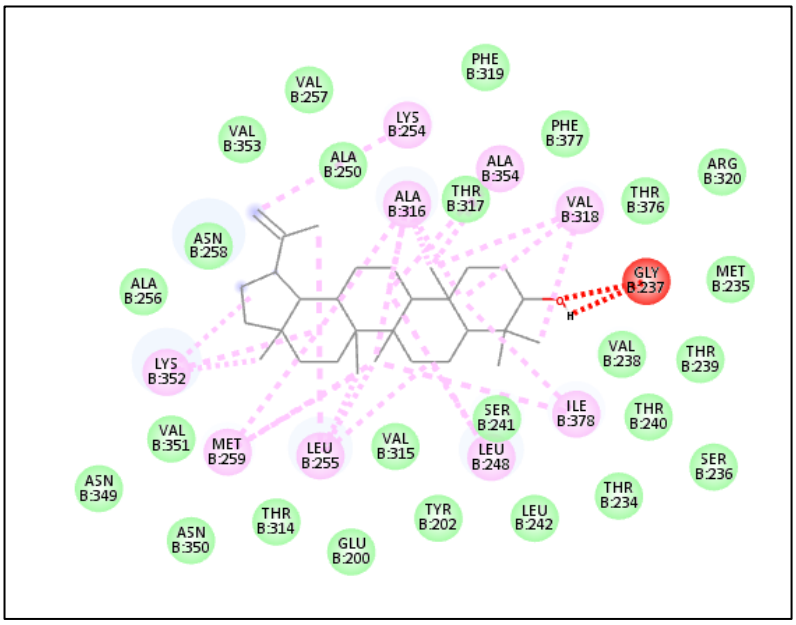


Figure 4: Two-dimensional binding interaction of lupeol with β tubulin receptor

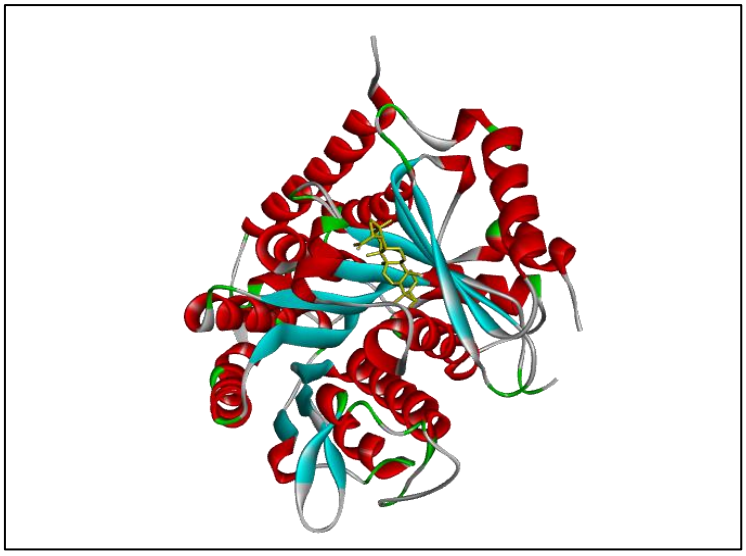


Figure 5: Three-dimensional binding interaction of lupeol with beta tubulin receptor

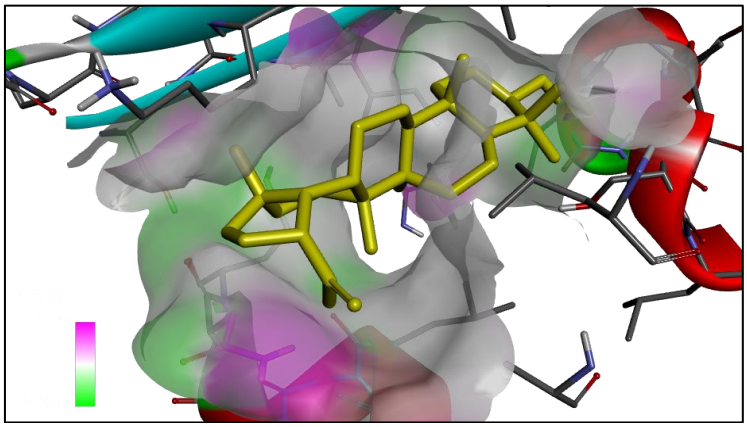


Figure 6: Binding conformation of ligand lupeol with beta tubulin receptor

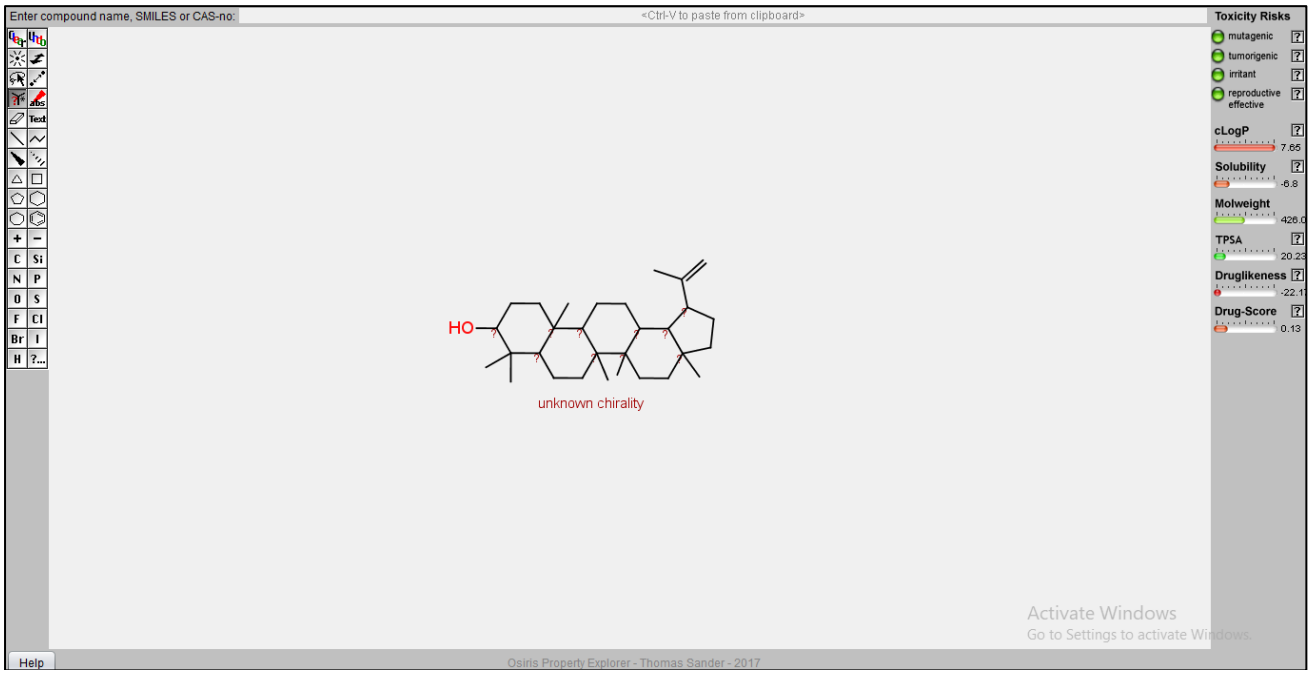


Figure 7: Pharmacokinetic and toxicity profiling of lupeol

Interactions

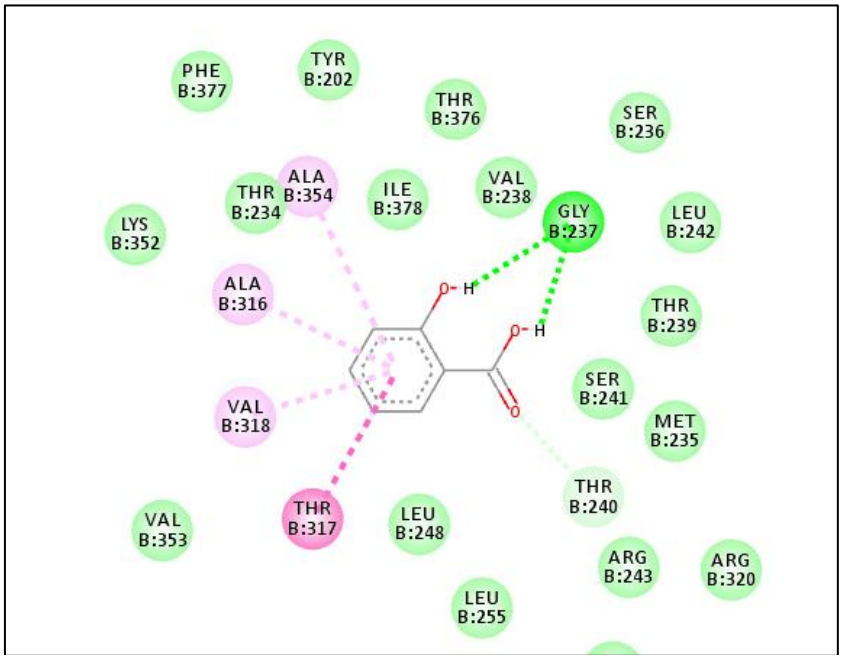


Figure 8: Two-dimensional binding interaction of salicylic acid with beta tubulin receptor

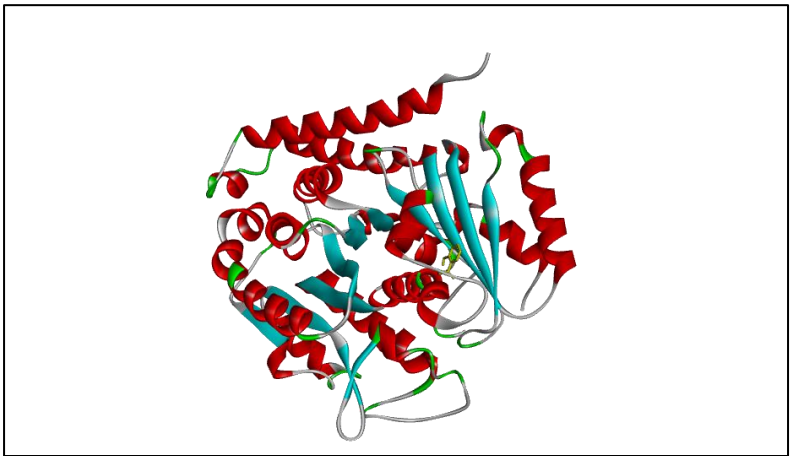


Figure 9: Three-dimensional binding interaction of salicylic acid with beta tubulin receptor

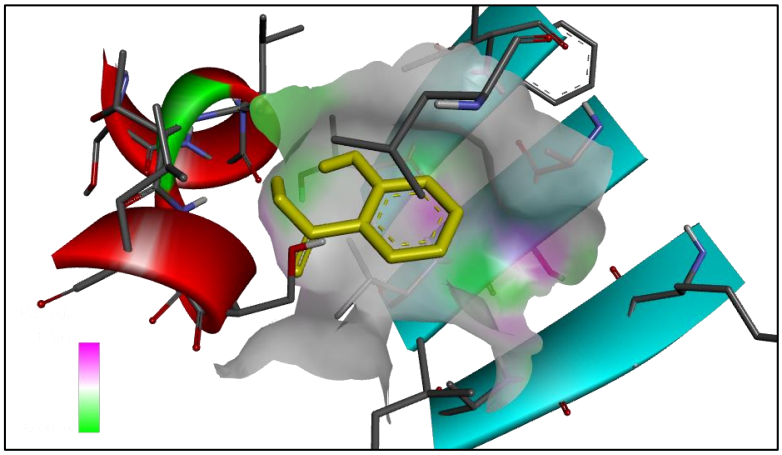


Figure 10: Binding conformation of ligand salicylic acid with beta tubulin receptor

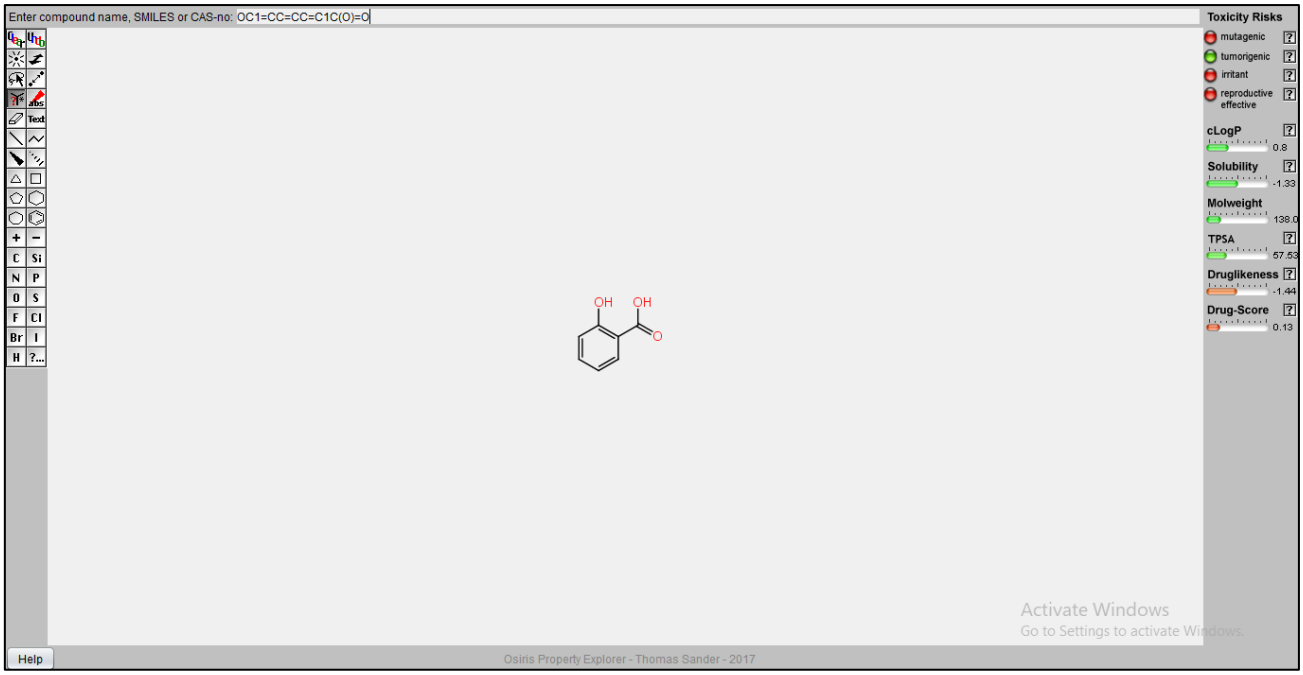


Figure 11: Pharmacokinetic and toxicity profiling of salicylic acid

RESULT AND DISCUSSION

Cleome viscosa Linn. (Capparidaceae), commonly known as "wild or dog mustard,"effective against fever, diarrhea, convulsion, boil. etc. In living beings, infection caused by helminths (helminthiasis) is a severe problem to health that results in hardship and stunted growth. In the developing world, helminthiasis (in human intestine) is the most common infectious disease. Presently helminths are resistant to commercially available medicinal agents and they are unaffordable too. The plants containing lupeol and salicylic acid are traditionally utilized for the anthelmintic property from the immortal time. The exact mechanism of action for the anthelmintic response of lupeol and salicylic acid was still not revealed. With intent to propose the most probable mechanism of action of lupeol and salicylic acid the docking based computational analysis has been performed against the beta tubulin receptor. The docking analysis, chemical interactions, followed by the physicochemical based pharmacokinetic profiling has revealed that the salicylic acid is executing its anthelmintic response via inhibiting the β- tubulin receptor. The molecular docking result revealed that salicylic acid and Lupeol showed encouraging docking score. The docking score found to be -1.98 and -3.82 kcal mol^{-1} respectively. The result was tabulated in table 1 & fig. 1-6 and 8-10.

The pharmacokinetic profiling of the lupeol ligand has revealed that it is having good pharmacokinetic profile without presence of any associated serious toxic effects. The pharmacokinetic and toxicity profiling results of lupeol was shown in figure 7. The pharmacokinetic profiling of the salicylic acid ligand has revealed that it is having good pharmacokinetic profile but having the presence of associated serious toxic effects like mutagenicity, irritant effect as well as reproductive effects. The pharmacokinetic and toxicity profiling results of salicylic acid was shown in figure 11.

CONCLUSION

Salicylic acid and Lupeol was present in ethyl acetate extract as per literature survey. Molecular docking of these active compounds with β-tubulin was carried out to illustrate the proposed mechanism of action. Inhibition of β - tubulin of the helminths can severely affect their vital cellular functions such as mitosis, motility, and transport. Therefore, in order to rationalize the anthelmintic activity of the active compounds present in ethyl acetate seed extract of *Cleome viscose* and understand their possible interactions, molecular docking simulation of the compounds have been carried out against β -tubulin. The anthelmintic potential of *Cleome viscose* seed was due to synergetic effect of salicylic acid and lupeol *via* inhibition of the β -tubulin of the helminthes.

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