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Original Research Article

Exploration of Mechanistic Insight Cutaneous Wound Repair of Lupeol Against Gskβ-3 Protein: Molecular Docking

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Abstract: ***Background:*** Cutaneous wound healing is a vital physiological process that involves the cooperation of several types of cells and their substances. The process of repairing the damage caused by a local injury starts at an early stage of inflammation. Ultimately, they lead to repair, which involves the replacement of specialized structures due to the deposition of collagen, and regeneration, which refers to the process of cell growth and subsequent differentiation from existing cells in the tissue and/or stem cells. Two These methods are not mutually exclusive. After a skin lesion, both regeneration and repair can occur in the same tissue, depending on the specific cell strains affected by the injury. ***Method:*** The present study aimed to identify protein inhibitors for glycogen synthase kinase-3 β (GSK-3 β) utilizing a molecular docking method. The binding was found using the Auto Dock software, which employed a grid-based docking approach. The 2D structures of compounds were created using the Merck Molecular Force Field (MMFF), which were then translated to 3D and energetically minimized with an arms gradient of 0.01. ***Results:*** The molecular docking analysis indicated that lupeol exhibited a highly favourable docking score. The docking score was determined to have a binding energy of -9.55 kcal/mol. ***Conclusion:*** The investigation's results showed that the lupeol had potent inhibitory action on *GSK-3 β* resulted in considerable wound healing efficacy.

Keywords: Wound healing, *In-silico* molecular docking, glycogen synthase kinase-3β (GSK-3β) protein & lupeol.

INTRODUCTION

Wound healing is an intricate, tightly regulated process that is critical to maintaining the barrier function of skin along with preserving all other skin functions. This process can be influenced by a variety of modifiable and nonmodifiable factors. As wound healing takes place in all parts of the human body, this review focuses on cutaneous wound healing and highlights the classical wound healing phases. Alterations in any of these phases can promote chronic wound development and may impede wound healing [1-3].

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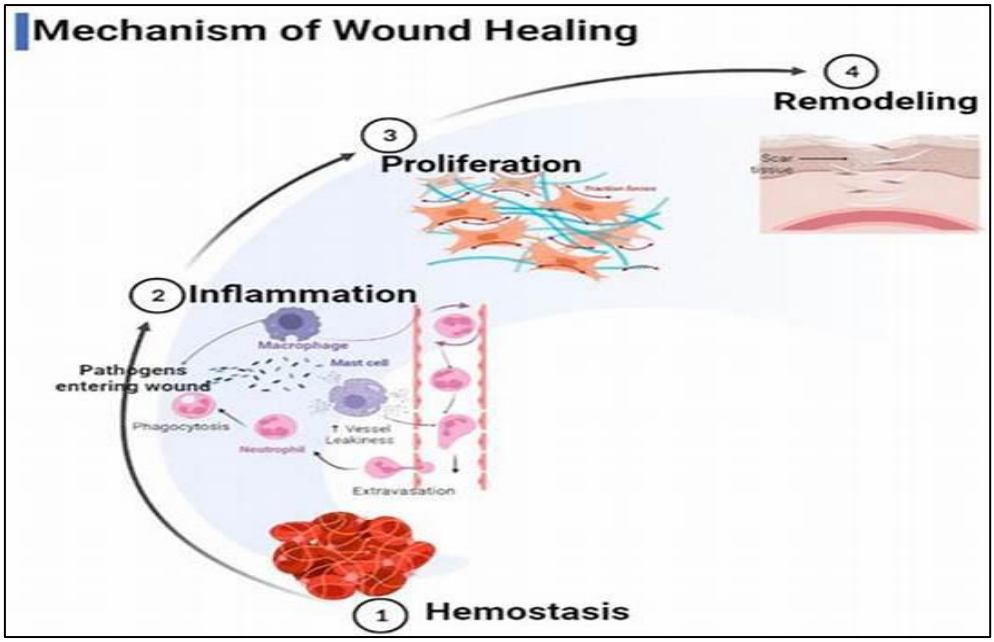


Phases of wound healing

Herbal medicines (HM), which are known as complementary and alternative medicines, have been used over the decades to treat medical ailments and promote wellness through their bioactive ingredients. Over time, humans have discovered which plant species are more effective as treatments for specific illnesses. The use of herbal medicine is a standard practice in traditional Chinese Medicine, Ayurveda, Unani, Russian herbalism, and other medical systems to apply botanicals topically to treat wounds and other dermatological problems [4].

There is a growing interest in natural triterpenoids, also known as phytosterols, due to their wide spectrum of biological activities. Triterpenes are a wide-spread group of natural compounds with considerable practical significance which are produced by arrangement of squalene epoxide in a chair-chair-chair-boat arrangement followed by condensation. Triterpenes are important structural components of plant membranes, and free triterpenes serve to stabilize phospholipid bilayers in plant cell membranes just as cholesterol does in animal cell membranes. Most triterpenes contain 28 or 29 carbons and one or two carbon-carbon double bonds, typically one in the sterol nucleus and sometimes a second in the alkyl side chain [5]. Triterpenes are natural components of human diets. The chemical formula of Lupeol is $C_{30}H_{50}O$ and its melting point is 215–216 °C. Properties computed from the structure of Lupeol show that it has a molecular weight of 426.7174 [g/mol], H-Bond donor 1, H-Bond acceptor 1, rotatable bond count 1, exact mass 426.386166, mono isotopic mass 426.386166 [6].

Experimental Works

Ligand Preparation:

2D Structure of lupeol was drawn using ChemSketch [6], the two-dimensional structure of the prepared ligand was converted into their 3-D structures optimized with 3D geometry. The optimized structure was saved in PDB format for AutoDock compatibility. The basic structures of the prepared ligand were given below:

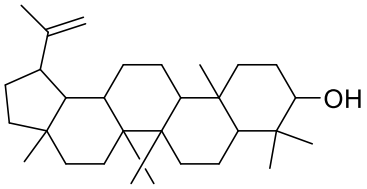


Figure 1: 2D structure of lupeol

Preparation of the grid file

The regions of interest used by Autodock 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 and grid points for the considered receptor in the current study are given in table 1 [7-8].

Table 1: Grid parameters used in current docking analysis of GSK3β receptor

S. No.	Receptor	x-axis	y-axis	z-axis	Spacing	x center	y center	z center
1	GSK3β	40	40	40	0.392	23.936	-17.104	9.189

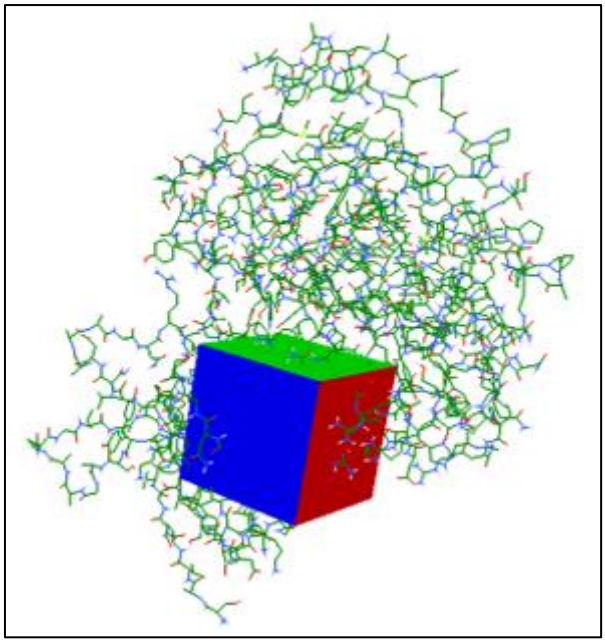


Figure 2: Grid box covering all active sites in GSK3β receptor

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 [9].

Docking Study

Crystal structure

The crystal structure of the protein consisting of GSK3β receptor is downloaded from the Protein Data Bank portal. All the primary information regarding all the receptor's structure was registered in the Protein data bank [10-11]. The complex ligand was separated by using Chimera software for all the target receptors.

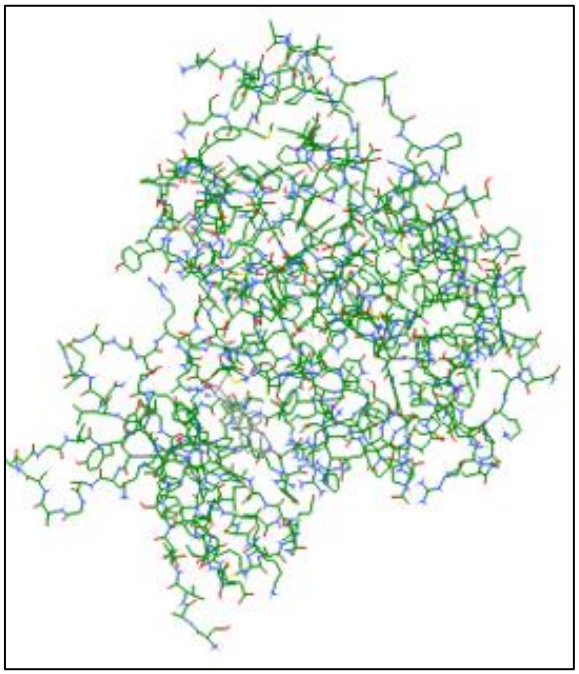


Figure 3: Crystal structure of GSK3β receptor (PDB ID-7oy5)

Processing of Protein

All the downloaded receptor proteins are having only one chains, i.e. chain A, which has been selected for experimental purpose and complex ligand was removed from it. The bound ligand was separated from the macromolecular complex by using software Chimera [12-14].

Molecular Docking Simulation Studies

Docking of ligand lupeol against GSK3β receptor was performed by Autodock. All the bonds of each ligand were kept flexible, while no residues in receptor were made flexible [15-18].

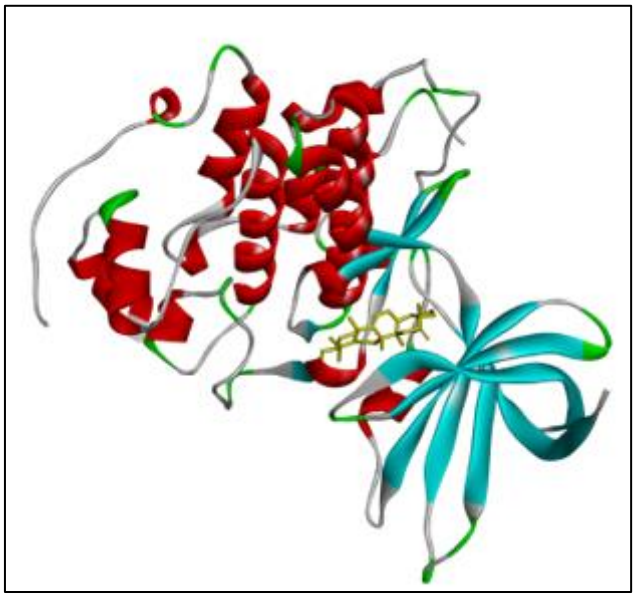


Figure 4: Binding mode of lupeol within the active site of GSK3β receptor

Toxicity & ADME-T Studies

The ligand molecules viz. lupeol 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 [19].

RESULTS AND DISCUSSION

Computer-Aided Drug Design (CADD) has emerged as an efficient means of developing candidate drugs for the treatment of many disease types. Applications of CADD approach to drug discovery are progressing day by day. The recent tendency in drug design is to rationally design potent therapeutics with multi-targeting effects, higher efficacies, and fewer side effects, especially in terms of toxicity. Terpenoids, the most abundant compounds in natural products, are a set of important secondary metabolites in plants with diverse structures. Terpenoids play key roles in plant growth and development, response to the environment, and physiological processes. As raw materials, terpenoids were also widely used in pharmaceuticals, food, and cosmetics industries. Terpenoids possess antitumor, anti-inflammatory, antibacterial, antiviral, antimalarial effects, promote transdermal absorption, prevent and treat cardiovascular diseases, and have hypoglycemic activities.

The scientific validation of the current investigation was done by computational based molecular docking study of lupeol against ***GSk-3β*** enzyme.

Inflammation, matrix deposition, cell proliferation, tissue modelling, collagenation, and epithelialization are all components of the orderly and coordinated process of healing a wound as per 2012, Soni H *et al.,* It has been discovered that the glycogen synthase kinase-3 (GSK-3) protein, an important regulatory enzyme, is inhibited by the Wnt/b-catenin pathway, which promotes wound healing. It has been investigated whether a range of medicinal plants could serve as potential sources of medications that treat wounds. We performed an *in-silico* screening of the phytoconstituents lupeol against *GSk-3β* enzyme.

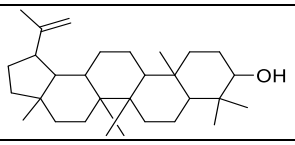
Lupeol found to be effective wound healing agent *via* binding to the target protein *GSk-3β* enzyme with binding energy -9.55 kcalmol^{-1}. The result was tabulated in table 2. The ki and IC50 was found to be 99.11nM & 0.0106 respectively (table 3). The binding mode of selected lead molecules showed in fig.4. The 2D and 3D interaction of selected compound displayed in fig.5 & 7. The interaction of lupeol with active site at *GSk-3β* enzyme showed as follows:

Compound	Pi-Alkyl	Pi-Pi bounding	Covalent bounding	Week Vander's interaction
Lupeol	Phe^{67} Val^{110} Leu^{132} Ala^{83} Leu^{135}	Cys ^{199}	VAL^{70}	VAL^{135}, Asp^{181}, Lys^{183}, Asn^{186}, Gln^{185}, Asp^{133}, Tyr^{134}, Ile^{63}, Lys^{85} & Asp^{200}.

The pharmacokinetic profile reveals that it is having good pharmacokinetic profile but with the presence of any major toxic effects including mutagenicity, tumorogenicity and reproductive effects.

The pharmacokinetic and toxicity profiling of lupeol was shown in figure 6 & table 4-7. Theoretically, all the ligand molecules have shown encouraging docking score. And followed Lipinski rule of molecular docking.

Table 2: Results of docking of ligands like lupeol against GSK3β receptor

S. No	Compound Name	Structure	Binding energy
1	Lupeol		-9.55 (ki: 99.11nM)

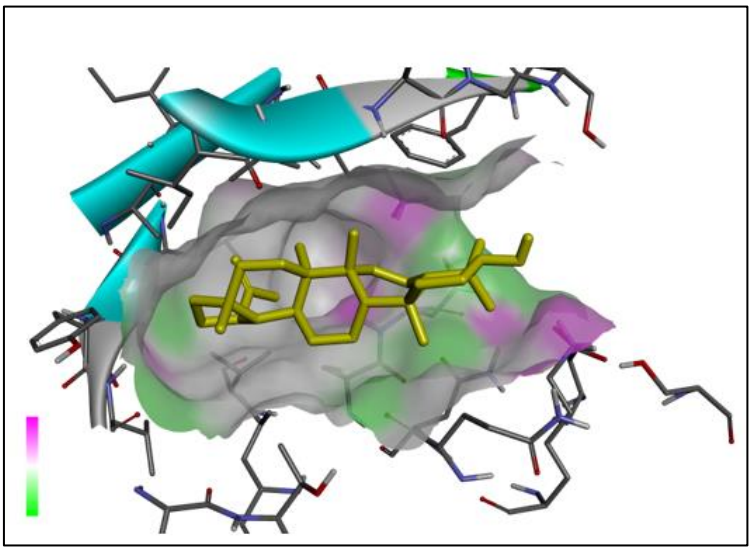


Figure 5: Three-dimensional binding mode of lupeol within the active site of GSK3β receptor

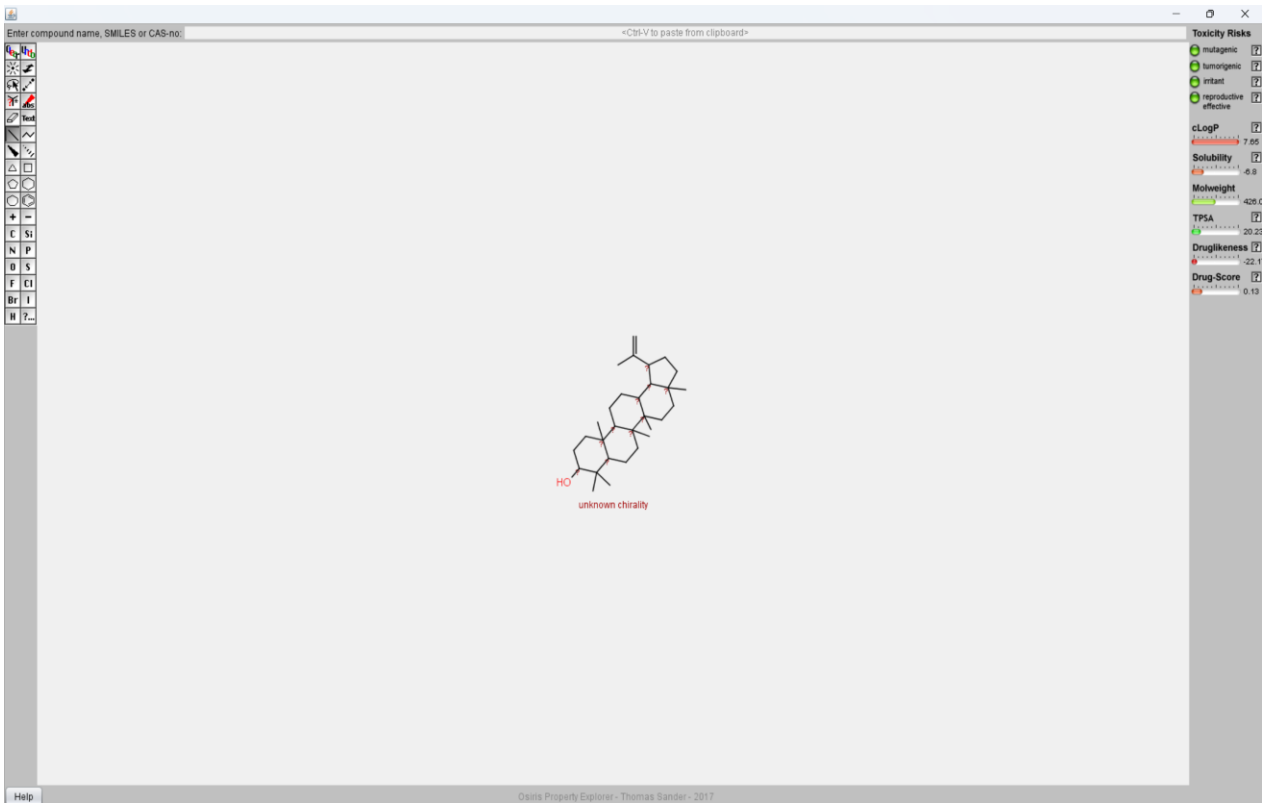


Figure 6: Pharmacokinetic and toxicity profiling of lupeol

Table 3: Determination of Ki value and IC50 value

S. No.	Compound	Ki	IC 50
1	**Lupeol**	99.11	0.0106

Table 4: Pharmacokinetic Profiling of lead molecules

Compound	ADMET			
	Mutagenic	**Tumorigenic**	**Irritant**	**Reproductive effectivity**
Lupeol	NO	NO	NO	NO

Table 5: Lipinski Properties of lead molecules

Compound	*cLogP*	Solubility	Mol.wt.	TPSA	Drug likeness	Drug score
Lupeol	7.65	6.8	426	20.23	22.1	0.13

Table 6: Drug likeness of lead molecules

Compound	Lipinski rule of five	H bond donar (<5)	H bond acceptor (<10)
Lupeol	Yes	1	1

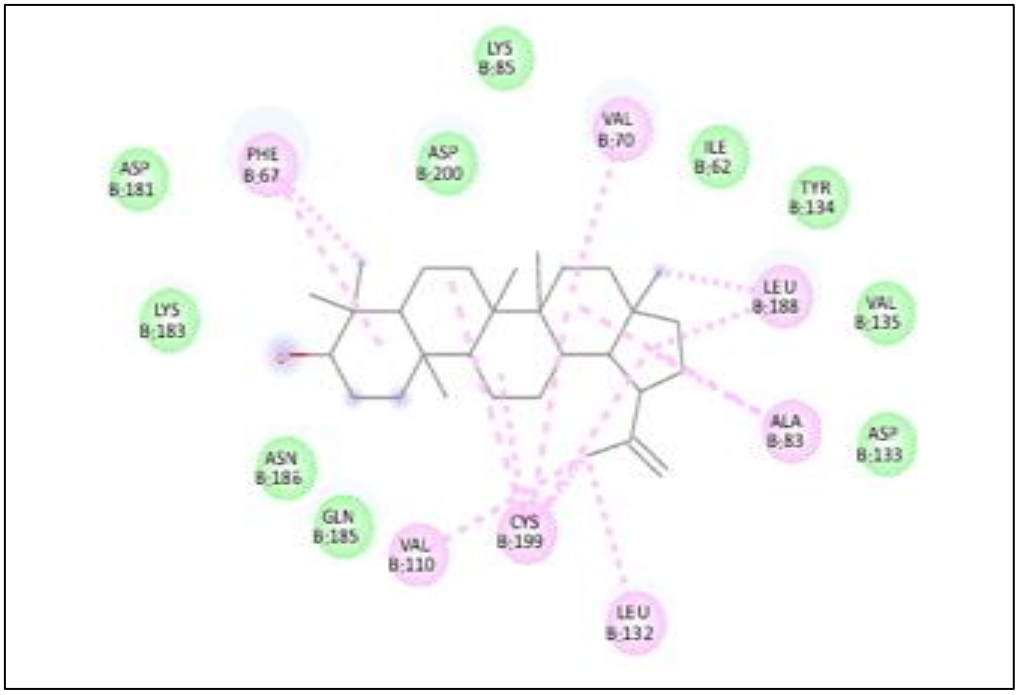


Figure 7: Two-dimensional binding mode of lupeol within the active site of GSK3β receptor

CONCLUSION

Small compounds like glycogen synthase kinase 3- (GSK3-) inhibitors may be useful tools for enhancing wound healing, according to prior research utilising a variety of animal models. It was discovered through a computationally based docking analysis that lupeol exhibit strong *GSK3*- β inhibiting effects. The results demonstrated a promising docking score and lead molecule's pattern of binding to the target protein's active region with strong covalent bonding.

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