

Research Article

Molecular Docking Analysis to Evaluate the Wound Healing Potential of Tamarindus Indica Extract

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Abstract:

In recent years, researchers have focused increasingly on the potential of several natural extracts to speed wound healing. The proteins involved in the wound healing process are the focus of this research, which uses a *tamarindus indica* bark. The purpose of this research is to examine determine the qualitative phytochemical screening and the potential inhibitory impact of phytochemicals in the extract on a panel of wound-healing proteins. Docking analysis with co-crystallized complexes of matrix metalloproteinase 2 (1GKC), transforming growth factor- (1PY5), fibroblast growth factor (1BFB), vascular endothelial growth factor receptor (3HNG), and IL-6 protein (4CNI) suggests that the fresh extract may have wound-healing properties. The GC-MS technique was used to determine the identity of the extract's active components. The molecular docking method was used to examine the active components based on their ability to interface with the target protein. This docking research demonstrates the binding affinity of *Tamarindus indica* bark extract to five distinct types of proteins. Interaction between ligands with MMP-9, the Best docking energy was found for (-7 Kcal/mol) 1h-pyrrole, Interaction between ligands with TGF- β (1PY5), the Best docking energy was found for (-8.3 Kcal/mol) 1,6-cyclodecadiene, Interaction between ligands with FGF-2 (1BFB) the best docking energy was found for (-4.4 Kcal/mol) 1-hexyl-2-nitrocyclohexane, Interaction between ligands with VEGF (3HNG) The best docking energy was found for (-7.8 Kcal/mol)(z,z)-.alpha.-farnesene. and Interaction between ligands with IL-6(4CNI) the best docking energy was found for(-5.4 Kcal/mol) Tetracyclo[6.1.0.0(2,4).0(5,7)].

Key words: *Tamrindus indica* bark, Phytochemical screening, Docking study for wound healing.

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INTRODUCTION:

Ancient time to till now, herbal plants are used in the treatment of many diseases and disorder, since it contains less side effects and adverse effect, and also low cost in compared to other medicines. As per WHO report 80% of people used has primary health care treatment of herbal medicine¹. In the developed countries, 25 per cent of the medical drugs are based on plants and their derivatives. A group of World Health Organization (WHO) experts, who met in Congo Brazzaville in 1976, sought to define traditional African medicine as 'the

sum total of practices, measures, ingredients and procedures of all kinds whether material or not, which from time immemorial has enabled the African to guard against diseases, to alleviate his/her suffering and to cure him/herself'. The skin is considered the largest organ in the human body with several essential functions. It protects the body from the outside environment, acts as the first line of defense against the entry of microorganisms, as well as a barrier to the loss of fluids, and assists in the regulation of body temperature.¹⁻³ When a disruption of the anatomical structure of the skin occurs, a

complicated and multifactorial process known as wound healing occurs. It is distinguished by a series of events, including inflammation, proliferation (neo-angiogenesis, granulation, re-epithelialization), and finally, maturation with scar remodeling (cicatrization).

Wound healing refers to the body's replacement of destroyed tissue by living tissue³⁸. Can be achieved by 2 processes; tissue regeneration & scar formation. Dynamic balance between these 2 is different in different tissues. The wound healing occurs in four phases such as haemostasis phase, inflammation phase, proliferation phase and remodeling phase.

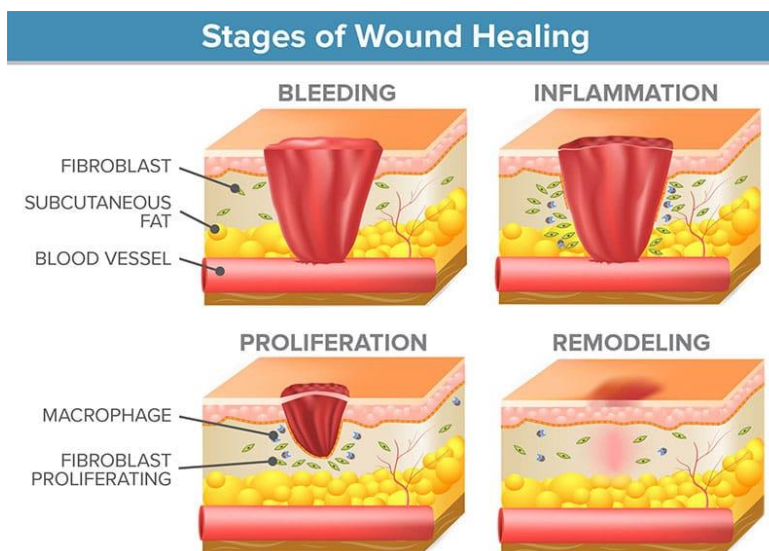


Figure 1: Structure of Wound Healing

1. Haemostasis phase (0 to few minutes)

In this stage formation of clots occurs to stop the bleeding.

2. Inflammation phase (0 to 3 days)

In this phase the wound exudates and become swell, warm and reddish in colour.

3. Proliferation phase (3 to 12 days)

In this phase many cells are accumulated together and profuse to form new tissue.

4. Remodeling phase (3 days to 6 months)

This is final stage the wound gets fully closed and the formation scar occur.

Active molecules from tamarindus indica extract were analyzed for their binding abilities with their respective targets using molecular docking. Potential wound healing activity of fresh extract shown by docking analysis with co-crystallized complexes of matrix metalloproteinase 2 (PDB ID:1GKC), transforming growth factor- β (PDB ID:1PY5), fibroblast growth factor (PDB ID:1BFB), vascular endothelial growth factor receptor (PDB ID:3HNG), and IL-6 protein (PDB ID:4CNI).

MATERIAL AND METHODS

Plant Material :

The whole plant of Tamarindus indica (Bark) was collected from nallanpillaipetral village which was 5km away from thiruvannamalai.

Chemicals requirement :

The chemicals and reagents used in the project work which are procured from Smt gandhimathi college of pharmacy Lab.

Preparation of Extract:

The well condition of tamarindus indica (Bark) was collected by using knife and hand picking method. After that bark should washed with fresh water to remove foreign substances. Then it was dried under the room temperature 72 degree fahrenheit for 2-3 days and Fumigated (to destroy the pest). Bark was powdered by pulverizer and sieve with 40 mesh size. Take 5kg of powdered drug which are suggested to the successive soxhlet extraction with Ethanol solvents for a periodic time (48hrs). The crude extract of tamarindus indica was filtered by using the muslin cloth (to prevent the wastage of crude drug) and separated and dried by using steam distillation. The crude drug were involved in the phytochemical investigation.

The active compounds present in the ethanolic extract of tamarindus indica were identified and confirmed by various qualitative, phytochemical investigations such as flavonoids, alkaloids, glycosides saponins, tannins, phytosterols, terpenoids and corresponding biological activities of those compound have supported in the process of wound healing. The fresh extract was subjected to GC-MS studies. Then the GC-MS reported compound was studied for assessment of wound healing potential.

GC-MS analysis:

The Clarus 680 GC was used in the analysis employed a fused silica column, packed with Elite-5MS (5% biphenyl 95% dimethylpolysiloxane, 30 m $\times$ 0.25 mm ID $\times$ 250 μ m df) and the components were separated using Helium as carrier gas at a constant flow of 1 ml/min. The injector temperature was set at 260°C during the chromatographic run. The 1 μ L of extract sample injected into the instrument the oven

temperature was as follows: 60 °C (2 min); followed by 300 °C at the rate of 10 °C min⁻¹; and 300 °C, where it was held for 6 min. The mass detector conditions were: transfer line temperature 240 °C; ion source temperature 240 °C; and ionization mode electron impact at 70 eV, a scan time 0.2 sec and scan interval of 0.1 sec. The fragments from 40 to 600 Da. The spectrums of the components were compared with the database of spectrum of known components stored in the GC-MS NIST (2008) library.

Gas chromatography study includes the important optimization process such as i) introduction of sample extract onto the GC column, ii) separation of its components on an analytical column and iii) detection of target analysis by using mass spectrometry (MS) detector. 5 ml of sample was evaporated to dryness and reconstituted into 2 ml methanol. The extracts were then subjected to GC-MS analysis. Chromatographic separation was carried out with instrument GC-MS-QP 2010 [SHIMADZU] instrument with Db 30.0 column (0.25 µm diameter × 0.25 µm thickness). The oven temperature was programmed from 70°C (isothermal for 5 minutes), with an increase of 10°C / min, to 200°C, then 5°C / min to 280°C, ending with a 35 minutes isothermal at 280°C. Mass spectra were taken at 70 eV; scan interval of 0.5 seconds

and scan range from 40–1000 m / z. Helium was used as the carrier gas at 99.99 % pressure with flow 1.0 ml / min and electronic pressure control on. Samples were dissolved in ethanol and injected automatically.

MOLECULAR DOCKING ANALYSIS

Ligands:

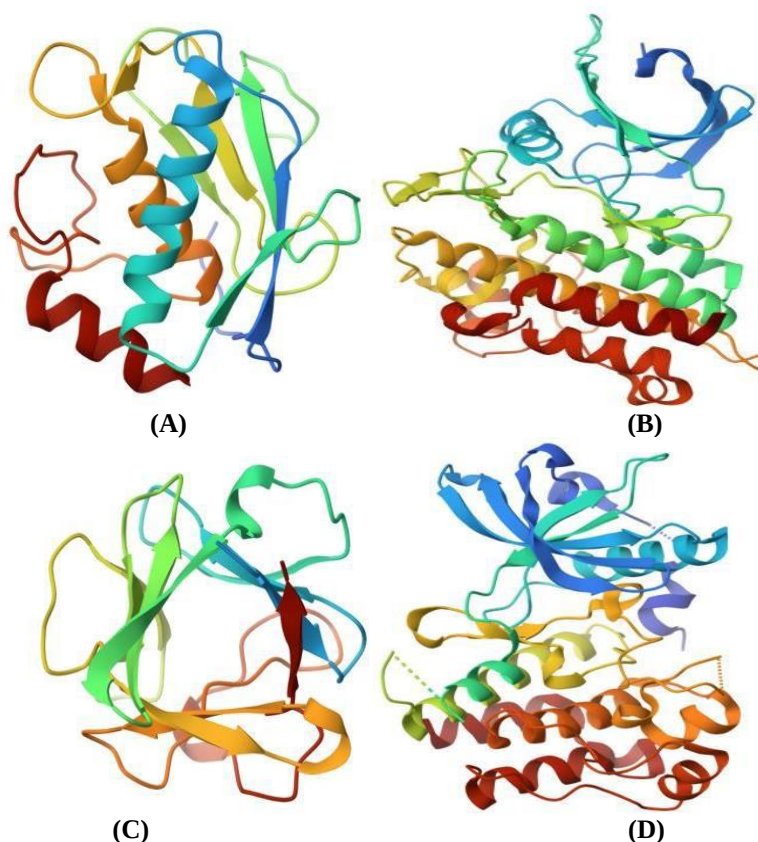
ligands were selected for the study and their 3D structures were downloaded from PubChem database in sdf format.

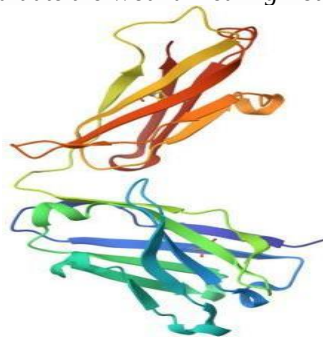
Protein Target:

3D structure of protein was procured from PDB. The protein structure was cleaned (water molecules and other hetero atoms removed), prepared and minimized before docking. The five selected protein is 1GKC (MMP9), TGF((1PY5), FGF 2 (1BFB), VEGF(3HNG) and IL 6 (4CNI)

Docking:

The binding site of the protein targets are defined. Molecular Docking was performed using MzDOCK to study interaction between the protein and ligand molecules. binding affinity of various ligands with protein were estimated.





(E)

(A) Docking with MMP9 (PDB ID: 1GKC), (B) Docking with TGF-beta receptor I kinase (PDB ID: 1PY5), (C) Docking with Fibroblast Growth Factor (PDB ID: 1BFB), (D) Docking with VEGFR1 (PDB ID: 3HNG), (E) Docking with IL-6 (PDB ID : 4CNI).

LIPINSKI'S RULE: ^{48,49}

Lipinski's rule of five is a concept frequently used in drug discovery. This rule helps to predict if a biologically active molecule is likely to have the chemical and physical properties to be orally bioavailable. The Lipinski rule bases pharmacokinetic drug properties such as absorption, distribution, metabolism and excretion on specific physicochemical properties such as:

- ❖ No more than 5 hydrogen bond donors

- ❖ No more than 10 hydrogen bond acceptors
- ❖ Molecular mass less than 500
- ❖ Partition coefficient not greater than 5
- ❖ Orally active drug can have no more than one violation

RESULT AND DISCUSSION

The consequence of tamarindus indica bark extract of phytochemical analysis, GCMS investigation, and molecular docking assement for wound healing effect

Table:1 Phytochemical Evaluation of Tamarindus indica extract:

S.NO	Chemical constituent	Ethanol extract
01	Alkaloids	-
02	Glycoside	+
03	Flavanoids	+
04	Anthroquinone	+
05	Phenols	-
06	Tannins	+
07	Saponins	+
08	Steriods	+
09	Terpenoids	+
10	Protein	-
11	Amino acids	+
12	Carbohydrates	-
13	Phytosterols	-

+ Positive, - Negative

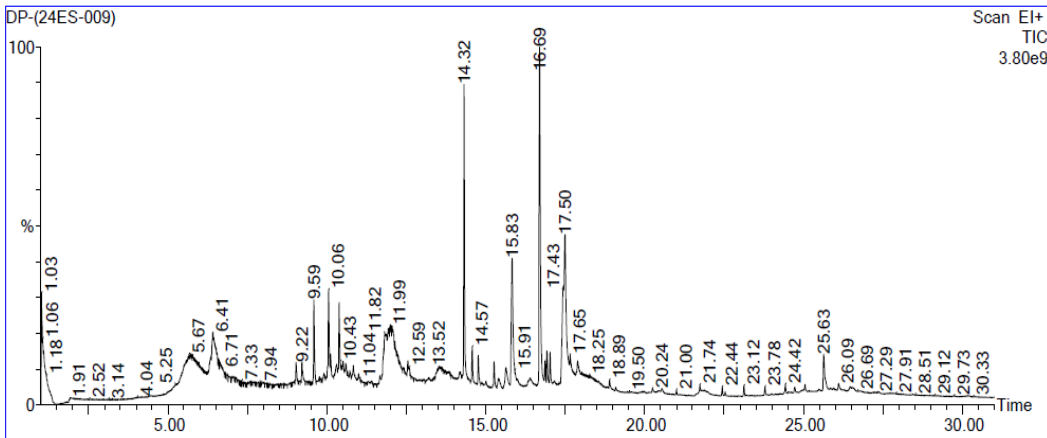


Figure 2: GC-MS analysis for ethanolic extract of Tamarindus indica extract
Table 2: ligands of ethanolic extract of Tamarindus indica

S.No	Compound Name	% of Peak Area	Retention time (RT)	Molecular formula (MF)	Molecular weight (MW)
1.	Isoxazolidine, 4-Ethyl-2,5-Dimethyl-, Cis-	16.312	5.730	C7H15ON	129
2.	Hydroperoxide, 1-Ethylbutyl	9.803	6.421	C6H14O2	118
3.	Tetracyclo[6.1.0.0(2,4).0(5,7)]Nonane, 3,3,6,6,9,9-Hexamethyl-, Cis,Cis,Tran	0.768	9.032	C15H24	204
4.	2-Methyl-6-Methylene-Octa-1,7-Dien-3-Ol	0.891	9.222	C10H16O	152
5.	(Z,Z)-.Alpha.-Farnesene	2.208	9.592	C15H24	204
6.	1,3,6-Octatriene, 3,7-Dimethyl-	2.153	10.057	C10H16	136
7.	1,6-Cyclodecadiene, 1-Methyl-5-Methylene-8-(1-Methylethyl)-, [S-(E,E)]-	1.846	10.387	C15H24	204
8.	Falcarinol	0.723	10.832	C17H24O	244
9.	Amyl Nitrite	4.140	11.823	C5H11O2N	117
10.	Cis-3-Hexenoic Acid	11.976	12.023	C6H10O2	114
11.	Octadecane, 1-Bromo-	0.865	12.548	C18H37Br	332
12.	2-Octylcyclopropene-1-Heptanol	7.043	14.319	C18H34O	266
13.	13-Tetradecene-11-Yn-1-Ol	0.880	14.574	C14H24O	208
14.	9,12,15-Octadecatrienal	1.391	15.634	C18H30O	262
15.	N-Hexadecanoic Acid	6.403	15.829	C16H32O2	256
16.	1h-Pyrrole, 1-(4-Methylphenyl)-	13.141	16.695	C11H11N	157
17.	9,12,15-Octadecatrienoic Acid, (Z,Z,Z)-	14.702	17.495	C18H30O2	278
18.	Oxirane, (7-Octenyl)-	1.780	17.650	C10H18O	154
19.	Pentanoic Acid, 2-(Aminooxy)-	1.282	17.890	C5H11O3N	133
20.	1-Hexyl-2-Nitrocyclohexane	1.695	25.629	C12H23O2N	213

Table 3:Structure of ligands in ethanolic extract of Tamarindus indica

S.No	Name of Ligands	Structure
1.	Isoxazolidine, 4-Ethyl-2,5-Dimethyl-, Cis-	
2.	Hydroperoxide, 1-Ethylbutyl	
3.	Tetracyclo[6.1.0.0(2,4).0(5,7)]Nonane, 3,3,6,6,9,9-Hexamethyl-, Cis,Cis,Tran	
4.	2-Methyl-6-Methylene-Octa-1,7-Dien-3-Ol	
5.	(Z,Z)-.Alpha.-Farnesene	
6.	1,3,6-Octatriene, 3,7-Dimethyl-	

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7.	1,6-Cyclodecadiene, 1-Methyl-5-Methylene-8-(1-Methylethyl)-, [S-(E,E)]-	
8.	Falcarinol	
9.	Amyl Nitrite	
10.	Cis-3-Hexenoic Acid	
11.	Octadecane, 1-Bromo-	
12.	2-Octylcyclopropene-1-Heptanol	
13.	13-Tetradec-11-Yn-1-Ol	
14.	9,12,15-Octadecatrienal	
15.	N-Hexadecanoic Acid	
16.	1h-Pyrrole, 1-(4-Methylphenyl)-	
17.	9,12,15-Octadecatrienoic Acid, (Z,Z,Z)-	
18.	Oxirane, (7-Octenyl)-	
19.	Pentanoic Acid, 2-(Aminooxy)-	

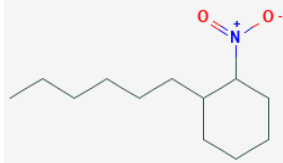
20.	1-Hexyl-2-Nitrocyclohexane	
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Table 4: Dock Binding energies of the ligands interact with proteins

	LIGANDS	MMP-9 (1GKC)	TGF- β(1PY5)	FGF-2 (1BFB)	VGEF (3HNG)	IL-6 (4CNI)
		Kcl/mol	Kcl/mol	Kcl/mol	Kcl/mol	Kcl/mol
A	Isoxazolidine, 4-ethyl-2,5-dimethyl-,cis-	-4.7	-4.8	-3.6	-5.3	-3.8
B	3-hexyl hydroperoxide	-5.1	-4.9	-3.3	-5.2	-3.7
C	Tetracyclo[6.1.0.0.0(2,4).0 (5,7)]nonane,3,3,6,6,9,9- Hexamethyl-,cis,cis,tran	-6.0	-7.4	-4.2	-6.3	-5.4
D	4.2-methyl-1-6-methylene-octa-1,7-dien-3-ol	-6.1	-5.7	-3.8	-6.0	-4.3
E	(z,z)-.alpha.-farnesene	-6.7	-6.6	-3.4	-7.8	-4.6
F	1,3,6-Octatriene,3,7-dimethyl-	-6.0	-6.0	-3.4	-6.4	-4.1
G	1,6-cyclodecadiene, 1-methyl 1-5-methylene-8-(1-methylethyl)-,[s-(e,e)]	-5.1	-8.3	-4.3	-6.7	-5.5
H	Falcarinol	-6.4	-6.7	-3.6	-7.4	-4.8
I	Amy nitrite	-4.7	-4.7	-3.4	-4.9	-3.7
J	Cis-3-hexenoic acid	-4.9	-4.7	-3.3	-5.1	-3.7
K	Octadecane,1-bromo-	-5.4	-5.9	-3.0	-6.2	-4.0
L	2-octylcyclopropene-1-heptanol	-5.9	-6.9	-3.7	-7.3	-4.9
M	13-tetradecene-11-yn-1-ol	-6.1	-6.3	-3.3	-6.3	-4.6
N	9,12,15-octadecatrienal	-6.1	-6.3	-3.1	-7.0	-4.9
O	N-hexadecanoic acid O-	-5.7	-6.1	-3.4	-6.7	-4.7
P	1h-pyrrol, 1-(4-methylphenyl)	-7.0	-6.7	-4.3	-7.1	-4.9
Q	9,12,15-Octadecatrienoic acid,(z,z,z)-	-6.2	-7.0	-3.7	-7.3	-4.9
R	Oxitane,(7-octenyl)-	-6.4	-6.5	-3.6	-6.6	-4.6
S	Pentanoic acid, 2-(amonoxy)	-5.1	-4.8	-3.6	-4.8	-4.2
T	1-hexyl-2-nitrocyclohexane	-6.4	-7.2	-4.4	-6.8	-5.3

Table 5. Lipinski rules of five

S.No	LIGANDS	Lipinskis rule				
		Molecular mass (<500)	Hydrogen bond donor(<5)	Hydrogen bond acceptor(<10)	High lipophilicity (<5)	Molar refractivity (40-130)
1	Isoxazolidine, 4-ethyl-2,5-dimethyl-,cis-	129	0	1	1.39	129.11
2	3-hexyl hydroperoxide	118	0	0	1.25	33.1
3	Tetracyclo[6.1.0.0.0(2,4).0 (5,7)]nonane,3,3,6,6,9,9- Hexamethyl-,cis,cis,tran	204	0	1	1.24	26.6
4	4.2-methyl-1-6-methylene-octa-1,7-dien-3-ol	152	0	3	1.46	41.47
5	(z,z)-.alpha.-farnesene	204	0	2	1.55	71.0
6	1,3,6-Octatriene,3,7-dimethyl-	136	0	0	1.19	48.96
7	1,6-cyclodecadiene, 1-methyl 1-5-methylene-8-(1-	204	0	1	1.32	68.5

	methylethyl)-,[s-(e,e)]					
8	Falcarinol	244	1	1	1.45	44.2
9	Amy nitrite	117	0	1	1.57	49.3
10	Cis-3-hexenoic acid	114	0	2	1.11	20.6
11	Octadecane,1-bromo-	332	0	4	1.30	46.7
12	2-octylcyclopropene-1-heptanol	266	0	0	1.56	57.0
13	15-tetradec-11-yn-1-ol	208	0	4	1.67	68.5
14	9,12,15-octadecatrienal	262	0	3	1.23	85.8
15	P-hexadecanoic acid	256	0	2	1.34	77.32
16	1h-pyrrol, 1-(4-methylphenyl)	157	0	1	1.29	69.9
17	9,12,15-Octadecaytenoic acid,(z,z,z)-	278	0	1	1.38	87.2
18	Oxitane,(7-octenyl)-	154	0	1	1.52	50.87
19	Pentanoic acid, 2-(amonoxy)	133	0	0	1.51	32.0
20	1-hexyl-2-nitrocyclohexane	213	0	2	1.22	61.6

1.Interaction between ligands with MMP-9 (1GKC)

The best possible ligand-MMP-9 Docking interaction were shown in Figure 3. Multiple metalloproteinase-9 (MMP-9) amino acid residues were identified as sites of ligand interaction in this diagram. Table 2 displays the ligand-MMP-9 interactions. Best docking energy was found for (-7 Kcal/mol) 1h-pyrrole, 1-(4-methylphenyl)-, (6.7 Kcal/mol) (z,z)-.alpha.-

farnesene and (-6.4 Kcal/mol) for 3 compounds such as Falcarinol, Oxirane, (7-octenyl), 1-hexyl-2-nitrocyclohexane. By reducing platelet aggregation and pro-inflammatory factors, increasing wound-site gelatin, collagen, elastin, and fibronectin, and facilitating a more rapid healing process, a model interaction between a ligand and the MMP-9 receptor has been proposed

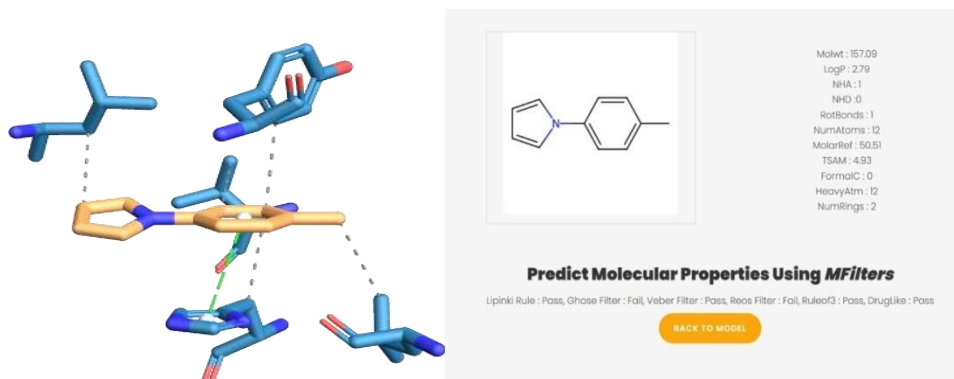


Figure 2: Best Scored Ligand: 1h-pyrrole, 1-(4-methylphenyl)-Binding Score = -7

2. Interaction between ligands with TGF- β (1PY5)

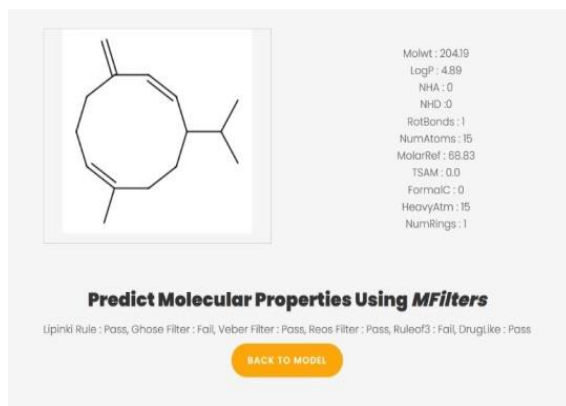
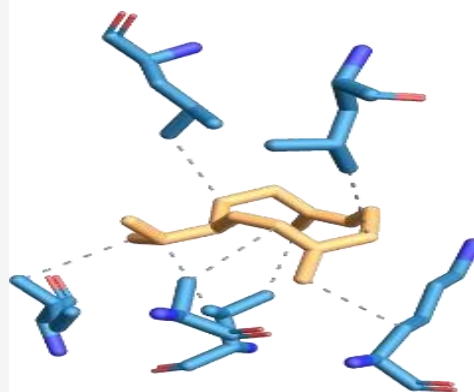


Figure 3: Best Scored Ligand: 1,6-cyclodecadiene, 1-methyl-5-methylene-8-(1-methylethyl)-, [s-(e,e)]- Binding Score = -8.3

The best possible ligand-TGF- β Docking interaction were shown in Figure 4. Amino acid residues were identified as sites of ligand interaction in this diagram. Table 2 displays the ligand interactions. Best docking energy was found for (-8.3 Kcal/mol) 1,6-cyclodecadiene, 1-methyl-5-methylene-8-(1-methylethyl)-[s-(e,e)], (-7.4 Kcal/mol) Tetracyclo[6.1.0.0(2,4).0(5,7)] nonane, 3,3,6,6,9,9-

hexamethyl-, cis,cis,tran, (-7.2 Kcal/mol) 1-hexyl-2-nitrocyclohexane and (-7.0 Kcal/mol) 9,12,15-octadecatrienoic acid, (z,z,z). TGF- β inhibits the translation of collagenases, enzymes that degrade collagen and the extracellular matrix. By increasing TGF- β expression, the extract of tamarindus indica promoted wound healing

3. Interaction between ligands with FGF-2 (1BFB)

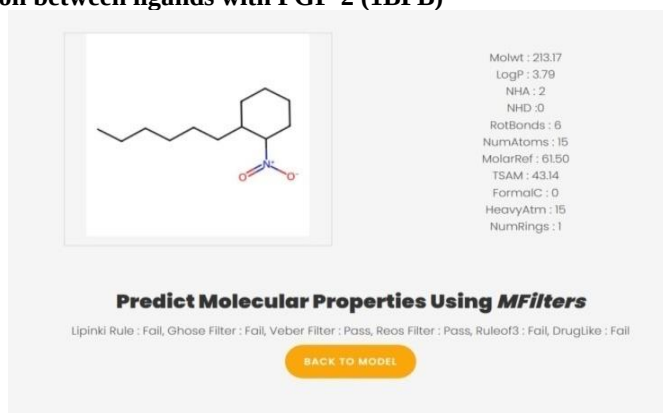
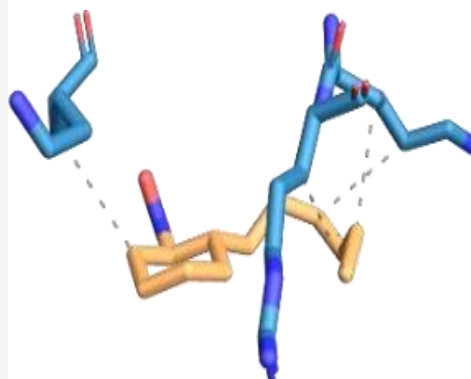


Figure 4: Best Scored Ligand : 1-hexyl-2-nitrocyclohexane Binding Score = -4.4

4. Interaction between ligands with VEGF (3HNG)

The best possible ligand-FGF Docking interaction shown in Figure 5. Amino acid residues were identified as sites of ligand interaction in this diagram. Table 2 displays the ligand-FGF interactions. The best docking energy was found for 1-hexyl-2-nitrocyclohexane and (-4.3 Kcal/mol) 1h-pyrrole, 1-(4-methylphenyl). Fibroblast binding interaction increases wound tensile strength. By contracting, myofibroblasts cause the wound to close and the fluid to be released, which causes the epidermis to stratify. Complete wound healing is the result of matrix remodeling and compositional confirmation inside the wound

The best possible ligand-VEGF Docking interaction are shown in Figure 6. Amino acid residues were identified as sites of ligand interaction in this diagram. Table 2 displays the ligand-VEGF interactions. The best docking energy (-7.8 Kcal/mol) was found for (z,z)-.alpha.-farnesene. The second best energy (-7.4 Kcal/mol) Falcarinol, (-7.3 Kcal/mol) 2-octylcyclopropene-1-heptanol. VEGF enhances wound healing by binding to two VEGF receptors that are expressed on vascular endothelial cells. These processes include the deposit of collagen and epithelialization. These results are consistent with the earlier findings that a ethanolic extract of tamarindus indica increased VEGF expression, leading to better wound healing

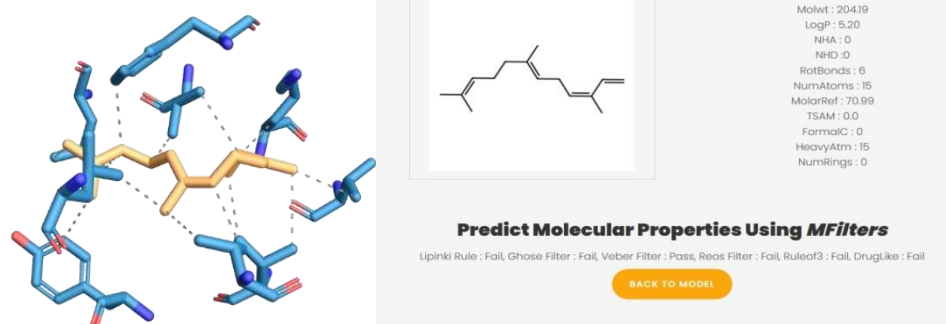


Figure 5: Best Scored Ligand : (z,z)-.alpha.-farnesene Binding Score = -7.8

5. Interaction between ligands with IL-6 (4CNI)

Figure 6 displays the best possible ligand-IL-6 docking interaction. Amino acid residues were identified as sites of ligand interaction in this diagram. Table 2 displays the ligand-IL-6 interactions. The best docking energy (-5.4 Kcal/mol) was

found for Tetracyclo[6.1.0.0(2,4).0(5,7)]nonane, 3,3,6,6,9,9-hexamethyl-, cis,cis,tran. Second best energy (-5.3 Kcal/mol) 1-hexyl-2-nitrocyclohexane. The inhibitory activity shown in the extract of Tmarindus indica was potential wound-healing activity.

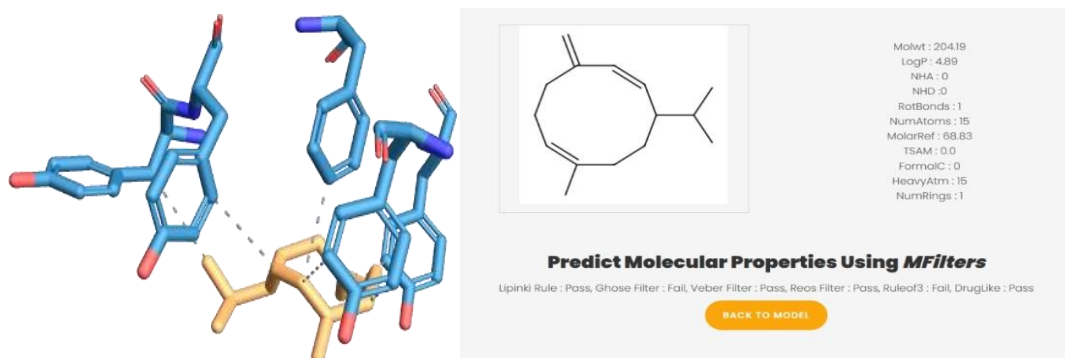
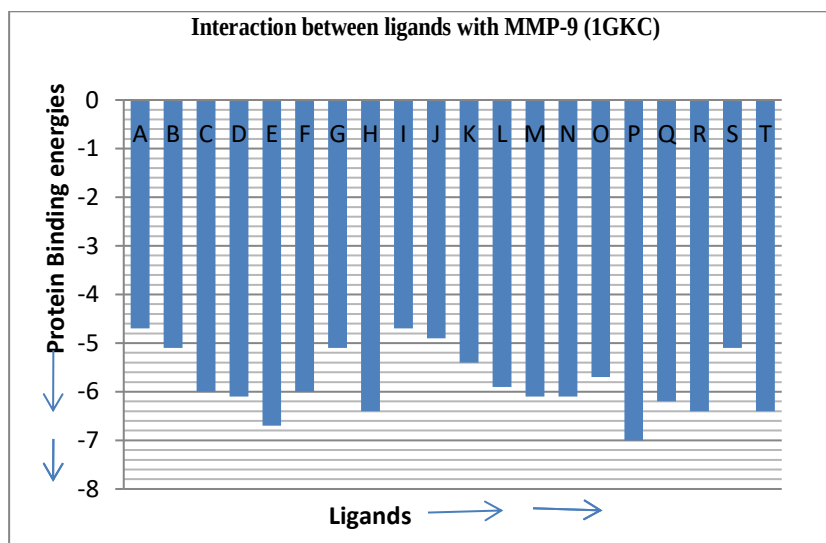
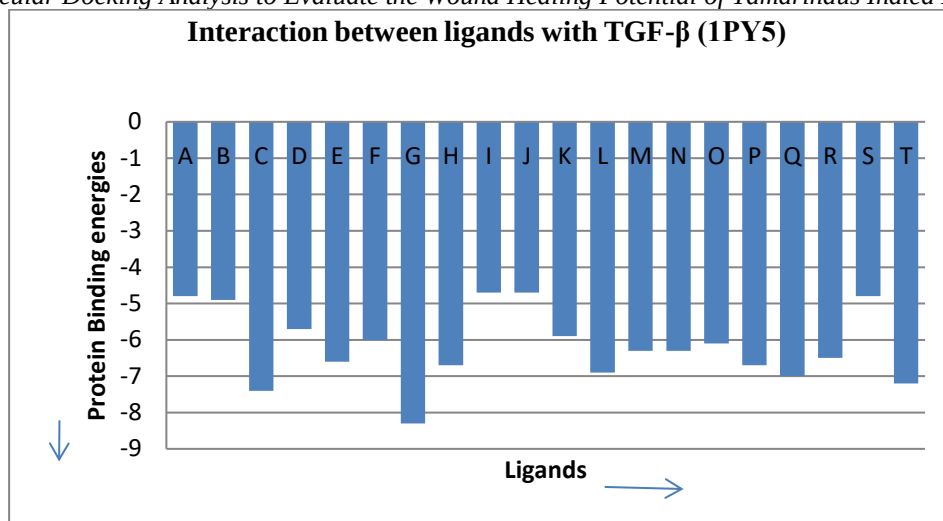
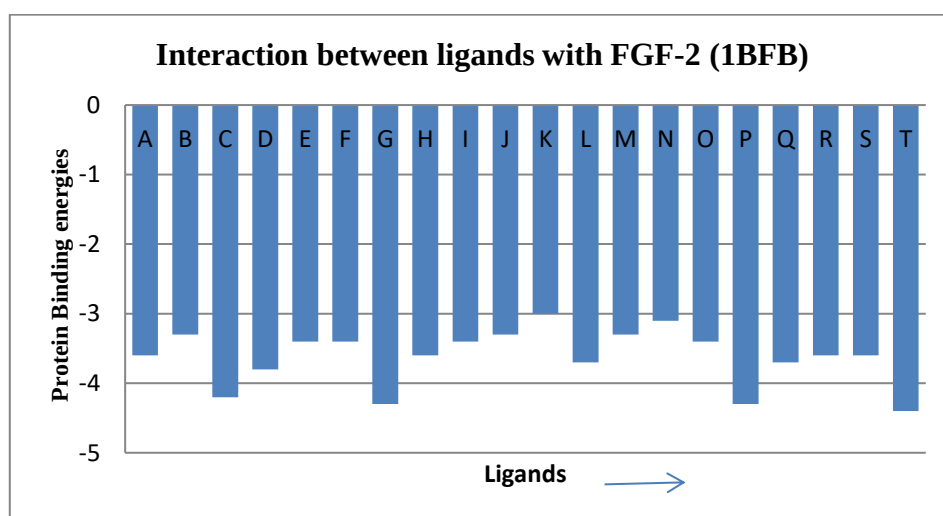
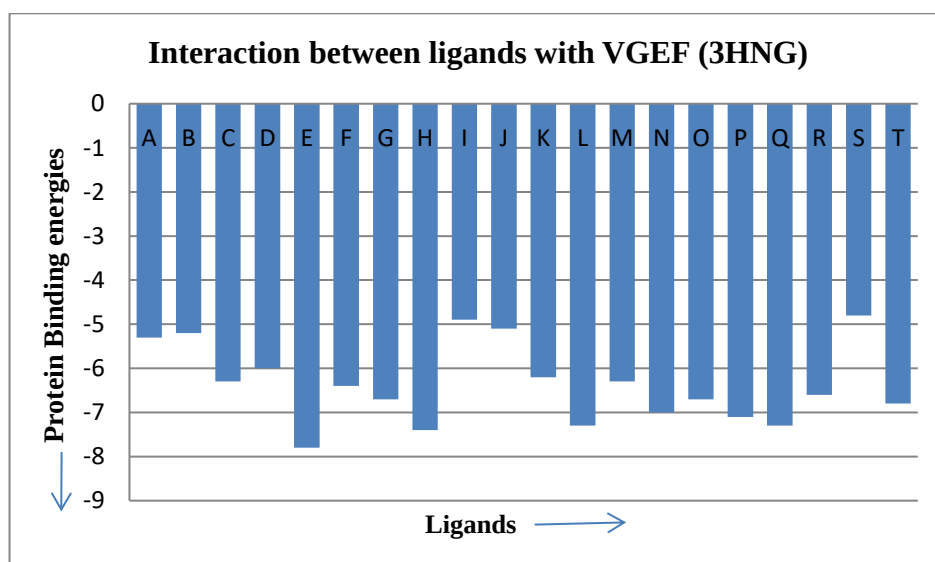
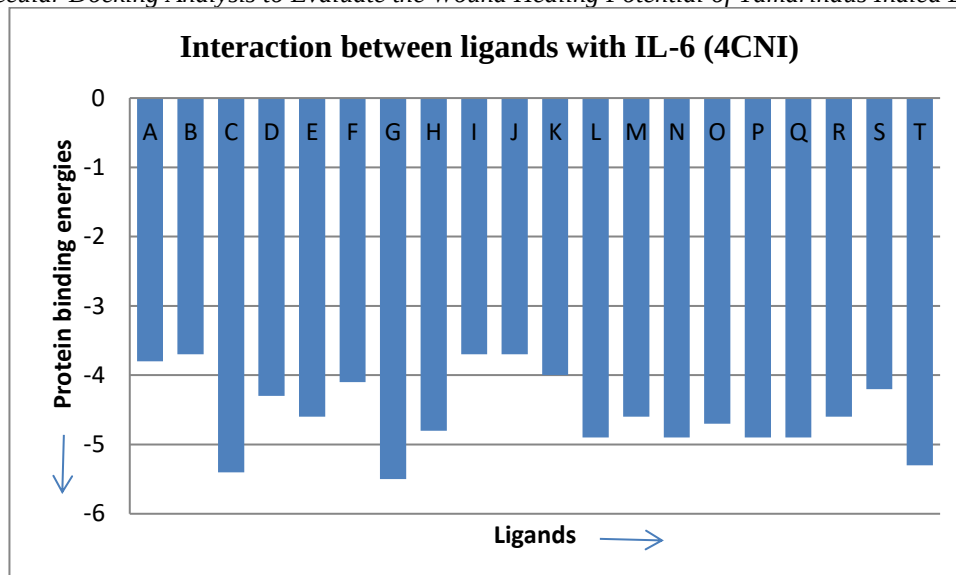


Figure 6: Best Scored Ligand : 1,6-cyclodecadiene, 1-methyl-5-methylene-8-(1-methylethyl)-, [s-(e,e)]-Binding Score = -5.5.







CONCLUSION

Finally we concluded the ethanolic extracts of *Tamarindus indica* bark present the phytoconstituent such as alkaloids, tannis, saponins, flavonoids, terpenoids, phenols, glycosides, anthroquinone, steroids, proteins and amino acids etc., Interaction between ligands with MMP-9, the Best docking energy was found for (-7 Kcal/mol) 1h-pyrrole, Interaction between ligands with TGF- β (1PY5), the Best docking energy was found for (-8.3 Kcal/mol) 1,6-cyclodecadiene, Interaction between ligands with FGF-2 (1BFB) the best docking energy was found for (-4.4 Kcal/mol) 1-hexyl-2-nitrocyclohexane, Interaction between ligands with VEGF (3HNG) The best docking energy was found for (-7.8 Kcal/mol)(z,z)-.alpha.-farnesene. and Interaction between ligands with IL-6(4CNI) the best docking energy was found for(-5.4 Kcal/mol) Tetracyclo[6.1.0.0(2,4).0(5,7)]. Finally we concluded the *tamarindus indica* ethanolic extract have excellent wound healing properties. From this docking studies outcome we further plan to *in-vitro* and *in-vivo* studies for ethanolic extract.

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CONFLICT OF INTERESTS

We have no conflict of interest.

AUTHOR CONTRIBUTIONS

All the authors equal contribution.

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