Original Article

Synthesis, Identification and *in-silico* Approach for wound Healing Potential in *Gnaphalium polycaulon* Extracts

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ABSTRACT

Aim/Background: The secondary metabolites can be identified from *G. polycaulon* and used as effective compounds for wound healing potential. The aims of the present study to identify the metabolites from *G. polycaulon* extracts by *in silico* study. **Methods:** The extraction of aqueous and methanolic *G. polycaulon* leaf extracts was subjected to characterization for silver nanoparticles. The phytoconstituents of the plant was analyzed by standard quantitative and quantitative methods. Then, the silver nanoparticles was synthesized and can be used for further *in silico* studies. Protein-ligand docking and modeling were studied by pharmacodynamics and kinetic study. **Results:** The identified bioactive metabolites were reported for *in silico* docking analysis. The similarity toolbox will give an easily utilized option for the identification of phytoconstituents with similar ligands based on a similarity score level. Greater interaction with target proteins has been observed for 2J67 (Toll-like receptor), 4MBS (Chemokine receptor), 1PWA (fibroblast growth factor), 4GR9 (melatonin receptor), 1A52 (estrogen receptor) and 2RH1 (adrenergic receptor) were docked with ligand from GC-MS compounds of selected test extracts and can easily find similarity score among all specific molecules in a simplified manner. **Conclusion:** the present study was the first report about the pharmacological activity of the *G. polycaulon* plant in the southern part of India. This plant possesses much beneficial ability due to bioactive phytocompounds. Thus, the present study concluded the ligands related to wound healing potential could be used for novel drug discovery in wound management.

Key words: *G. polycaulon*, Silver nanoparticles, Wound healing, GCMS, Protein ligands, *In silico* analysis.

INTRODUCTION

In the modern genomic era, there has been a massive outbreak of information about plants from various sources. In particular, there is a generation of experimental data from genomic analysis, gene sequencing, microarray data analysis and protein structural detection and analysis to be processed for the creation of useful information.[1-3] New drugs and therapeutic materials can be discovered easily, which can be used for human welfare. The small molecules or ligands with chemical compounds were used for curing wound healing related diseases against many targets.[4,5] The interaction profile information of ligands acts as a key and lock pattern to inhibit the action of various proteins with functions. A specific option is given to the user to use homology-modeling tools and find a similar protein structure for carried out the docking with similar ligands based on a similarity score. Molecular

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docking helps in the identification of an effective molecule for the targeted protein, related to the wound healing process. Specifically, natural plant products with potential biological properties were identified for the delivery of the targeted drug.[2,6] drug discovery is a quite interesting field to find new novel compounds for drug management.

Outstanding advances were organized in the field of biological sciences to hardness the benefit of life sciences and health care in wound management.[7] Many reports confirmed the utilization of the plants in wound healing from ancient times, especially about the mechanism of action, toxicity and efficacy of plant products.[8-10] Multifunctional phytoconstituents played a vital role in wound healing, inflammation and protein modeling. In particular, nanocrystalline silver may be involved in inflammatory events in the healing process and stimulates the early stages of wound healing. Therefore, silver nanoparticles possessed significant wound healing and anti-inflammatory activities.[11-13] The green synthesis technology was carried out in an eco-friendly manner for the synthesis of silver nanoparticles, which can produce only degradable materials. In the present study, we fabricated the silver nanoparticles as a green synthesis from Gnaphalium extracts.[14] The biological properties of the G. polycaulon extracts proved the significant effects. In addition, cytotoxicity of nanoparticles acts as an important factor for consideration as safety and excellent nanomaterials for various therapeutic potential.[15] Therefore, the green synthesis of the extract was investigated and examined the interaction with different proteins for the wound healing potential by using *in silico* molecular docking.[16]

New research with natural plants has become great interesting attention with safer herbal remedies and less damaging to the human body than synthetic drugs. The development of this research resulted in a huge effect on the pharmaceutical industry, showed promising interest in synthesizing metabolites from plants. In the recent survey, 5-10 % have been studied plant phytochemicals and validated the pharmacological results.[11,13,17] The fast-developing research tools offered unique opportunities to documented information and knowledge on medicinal and aromatic plants,[18] particularly from different traditional systems and folklore practices. The phytochemicals/bioactive compounds in *Asteraceae* plants act as a potential barrier against pathogenic organisms,[19] which either can be as one or combined formulations in the drug delivery.[20,21] Hence, medicinal plants can be used as disease curing agents for the verification of pharmacological effects.[19]

Many reports reported that folkloric medicinal plants of therapeutic potential belonged to the *Asteraceae* family.[22-25] In particular, *Gnaphalium* species have biological and therapeutic properties including antimicrobial, antioxidant, cytotoxicity, anti-inflammatory, anti-diabetic and wound healing.[20,26-30] Among many species, *G. polycaulon* was reported for the wound healing ability by the presence of major phytocompounds.[20,30] Tribal communities in the Kothagiri areas (The Nilgiri District, Tamil Nadu, India) followed the traditional practices of this plant for the healing of burns wounds.[20,23,31,32] *in silico* studies performed to evaluate the small molecules or ligands related to wound healing by using phytoconstituents of *G. polycaulon* extracts.[20,33] The molecular docking approach remains in the identification of unknown and secondary therapeutic targets of drugs from plants.[34]

GC-MC analysis of the various *G. polycaulon* extracts confirmed the identification of the major phytochemicals/bioactive components. Then, *in silico* studies were performed based on GC-MS results of the extracts with proteins related to the wound healing potential and ligands. The present study is the first report to validate the *in silico* analysis in identified phytoconstituents of *G. polycaulon* extracts.

MATERIALS AND METHODS

Collection and preparation of plant extracts

The plants were collected, identified and authenticated by the Madras Herbarium, as *Gnaphalium polycaulon* Pers. The healthy leaves were gently washed and processed for fresh and dried leaf samples. The soxhlet extraction was performed with forty grams of powdered samples and further concentrated by using a rotary evaporator. The supernatant was collected for further studies.

Synthesis of silver nanoparticles

The silver nanoparticles were synthesized by using the fresh and dried leaf extracts of *G. polycaulon*. The polymerization was carried out, which resulted in the soluble portion of plant extracts. The filtered supernatant was dissolved in 1% (1 mM) silver nitrate and incubated for 12 h in dark conditions for the visual observation of brownish color. Finally, centrifuged with a centrifuge machine (Thermo Scientific) and the supernatant was stored at 4°C for further studies. The selected extracts were an aqueous extract of fresh leaf, methanolic extract of dried leaf, synthesized silver nanoparticles from an aqueous extract of fresh leaf and methanolic extract of the dried leaf can be used for further studies.

Protein preparation

The structural data of small biological molecules was used for protein preparation in areas of structural biology. The 3-D structure of diseased protein such as 2J67 (Toll-like receptor), 4MBS (Chemokine receptor), 1PWA (fibroblast growth factor), 4GR9 (melatonin receptor), 1A52 (estrogen receptor) and 2RH1 (adrenergic receptor) were identified from Protein Data Bank (PDB) and selected.

Protein-ligand docking

The protein-ligand docking can be performed by using ligand preparation with the Schrodinger suite. This tool can be used mainly for manipulating chemical structures and analyzed the data. Therefore, the Lig Prep module was used to retrieve all molecules from GCMS results and docked with diseased protein. The complete interaction profile was analyzed based on the number of structures with tautomer, stereochemistry and ring conformations. Thus, the molecules can be selected including molecular weight and functional groups present in it.

Pharmacophore Molecular modeling

The next step was the pharmacophore molecular modeling methods. The method can be carried out with the PHASE 3.0 module to geometry optimization with the semi-empirical OPLS 2005 force field for the generation of 3D structures. Then, the prepared ligands were used for conformational analysis using Monte Carlo Multiple Minimum methods. Finally, the prepared ligands were selected and used for pharmacophore generation. The six pharmacophore sites were created based on the chemical structures of ligands including H-bond acceptor (A), H-bond donor (D), hydrophobic (H), negatively charged (N), positively charged (P) and aromatic ring (R) groups by using a tree-based partitioning technique. Then, the pharmacophores were scored and ranked with related to the active and non-active ligands.

Pharmacodynamics and kinetic study

The toxicity effect of the selected molecules from GC-MS analysis of the *G. polycaulon* extracts can be examined by using the QikProp module. Nearly 30 types of functional groups were docked with the ligands in the high-throughput screening (HTS) assays, which can easily be developed and employed QSAR/QSPR models to perform the similarity or diversity analysis. The retrieved protein can be prepared by using the Schrodinger protein preparation wizard, which is assumed as an initial protein structure in the PDB. The results can be confined and used with other Schrodinger products.

Protein-ligand interaction/docking process

In this process, grid files were used for attempting to dock with a ligand. The receptor was generated along with the structure from the receptor grid generation panel. After this process, the various stages were performed, which involves the molecular docking of the target protein with a ligand, importing the Prepared PAL132 protein domain, glide ligand docking and examining glide data.

RESULTS AND DISCUSSION

Ligand optimization from GC-MS results

GC–MS results of *G. polycaulon* extracts were found to be 96 molecules with molecular weight ranges from 78-792 g/mol. Among them, 126 molecules were identified from Chemical Abstract Services (CAS) in the PubChem deposition by removed repeated structures from GC-MS results.[12,35] The physical and surface properties were used for the determination of ligand structures with conformational positions.[36]

Ligand derived from CAS - PubChem

In specific, 126 molecules were easily derived from *G. polycaulon* extracts with the help of Pub Chem and CAS number retrieved from GC-MS. The selected ligands from various extracts including aqueous extract of the fresh leaf (51) with synthesized silver nanoparticles (28) and methanolic extract of the dried leaf (9) with synthesized silver nanoparticles (38). Therefore, further *in silico* studies were essential to evaluating the protein with the suitable structures from publicly available databases, which can interact with the diseased protein for the identification of the molecules.[4,37,38]

Toxicity prediction of a selected molecule

The toxicity of the selected molecules was checked for ADME properties initially by using the QikProp tool from the Schrödinger suite, which confirmed drug-like properties based on Lipinski's rule of five. Based on certain properties such as the molecular weight of less than 500 Da, the number of hydrogen bond donors of less than five and a hydrogen bond acceptor of less than 10, the predicted partition coefficient of less than five was evaluated.[34] The aqueous solubility (QPlogS) was found to be different for the determination of the absorption and distribution of the drug.[39] As a result, all the pharmacokinetics parameters confirmed that the molecules of the plant source fitted well with the acceptable range defined.

Pharmacophore site prediction

The interaction of ligand activity towards diseased protein can be analyzed based on the total number of

active groups present in the phytocompounds of plant sources. Phase modules were used to analyze the number of active groups occupied in the molecule. Positive and negative groups in a molecule are capable of inducing high-energy potential to its binding score. Based on the GC-MS profile of *G. polycaulon* extracts, the ligand was the more feasible mechanism that can interact with any protein of a high hydrophilic group in the polar surface area. The pharmacophores analysis showed that the screened molecules were highly viable bonds with both hydrophobic amino acids and hydrophilic acids from selected proteins.[1]

Docking of the target protein and screened ligand from pharmacophore actives

The selection of the target protein was retrieved from PDB and analyzed (Figure 1). Proteins such as 2J67 (Toll-like receptor), 4MBS (Chemokine receptor), 1PWA (fibroblast growth factor), 4GR9 (melatonin receptor), 1A52 (estrogen receptor) and 2RH1 (adrenergic receptor) interacted with 22 molecules. The compounds in aqueous extract of fresh leaf, methanolic extract of dried leaf, silver nanoparticles synthesized by aqueous extract of fresh leaf and silver nanoparticles synthesized by methanolic extract of dried leaf of *G. polycaulon* have interacted with six target protein receptors with binding energy were listed (Table 1), which was confirmed by assessed the Glide score range, which corresponds with diseased protein.[18,32]

The following results were reported with the interaction profile of the highest docked score from each protein. The interaction profile (Figure 2 and 3) of all proteins for the bioactive phytoconstituents from various extracts as follows: Aqueous extract of the fresh leaf (Table 2), methanolic extract of the dried leaf (Table 3), synthesized silver nanoparticles from an aqueous extract of the fresh leaf (Table 4) and methanolic extract of the dried leaf (Table 5). The Interaction profile of bioactive phytoconstituents from the various extract of *G. polycaulon* concerning the Toll-like receptor, 2J67; Chemokine receptor, 4MBS; FGF receptor, 1PWA; Melatonin receptor, 4GR9; Estrogen receptor, 1A52; Adrenergic receptor, 2RH1 were confirmed the hydro-oxy group interactions with proteins in the certain distance with oxygen atom from ligands. The interaction was confirmed the bond distances within the molecular mechanics property for each extract.[34,37]

Based on the GC-MS spectrum, 94 phytoconstituents have been selected from aqueous extracts of the fresh leaf (crude and with silver nanoparticles) and methanolic extracts of the dried leaf (crude and with silver nanoparticles). Among them, 126 selected

Table 1: Protein-Screened ligand docking from GC-MS of various extracts of *G. polycaulon*.

Protein Name	Screened Ligand	Glide Score
Aqueous extract of fresh leaf		
2J67	11-Piperidyl,9-Enol Pga1 (TMS)3	-5.69935
4MBS	6-(4-Chlorophenyl)-3-cyano-4-(N-benzylpiperazino)-2H-pyran-2-one	-8.423
1PWA	Pyrrolidine, 1-methyl-2-phenyl-3-(phenylsulfonyl)	-4.081
4GR9	Pyrrolidine, 1-methyl-2-phenyl-3-(phenylsulfonyl)	-4.861
1A52	2-(4-Aminophenyl)-5-hexynoic acid	-5.946
2RH1	5-Imino-7-phenyl-2,3-dihydro-5H-thiazolo[3,2-1]pyrimidine-6-carbonitrile	-6.326
Synthesized silver nanoparticles using aqueous extract of fresh leaf		
2J67	2-Benzyl-3-(4-methoxyphenyl)-6-chloro-7,8-dihydroisoquinolin-1(2H)-one	-5.203
4MBS	4,5-Bis(p-bromophenoxy)-1,2-dicyanobenzene	-7.436
4GR9	9,10-Anthracenedione	-3.254
1PWA	4-methoxycarbonylmethylthio-1-triisopropylsilylindole	-4.455
1A52	Methane, sulfinylbis	-4.543
2RH1	4,5-Bis(p-bromophenoxy)-1,2-dicyanobenzene.	-5.587
Methanolic extract of dried leaf		
2J67	6-[2-(3-Hydroxy-4-methoxyphenyl) ethyl]-4-methoxy-5,6-dihydro-2H-pyran-2-one	-5.062
4MBS	2-Pentyne-1,4-diol, 4-methyl-1-(2-thienyl)	-5.115
1PWA	4-methoxycarbonylmethylthio-1-triisopropylsilylindole	-4.455
4GR9	6-[2-(3-Hydroxy-4-methoxyphenyl) ethyl]-4-methoxy-5,6-dihydro-2H-pyran-2-one	-3.823
1A52	2,6,10,15,19,23-Hexamethyl-2,6,14,18,22-tetracosapentaene-10,11-diol	-2.527
2RH1	6-[2-(3-Hydroxy-4-methoxyphenyl) ethyl]-4-methoxy-5,6-dihydro-2H-pyran-2-one	-5.547
Synthesized silver nanoparticles using the methanolic extract of dried leaf		
2J67	Dihydrokhusilal Acid	-4.827
4MBS	4-Chloro-4-methylpentane-2,3-dione	-6.601
1PWA	Methanesulphinic acid methyl ester	-2.884
4GR9	Dihydrokhusilal Acid	-4.566
2RH1	6-Methyl-2-(4-nitrophenyl)-5-phenylthio-2,3-dihydro-4-pyrone	-5.878

Table 2: Interaction profile of bioactive phytoconstituents from aqueous extract of fresh leaf of *G. polycaulon*.

Proteins	Protein Complex	Amino Acid	Protein Atom	Ligand Atom	Bond Length	G Score	No of Hydrogen Bonds
Toll-like receptor, 2J67	11-Piperidyl,9-Enol PGA1 (TMS)3	LEU 727	O	H	2.28	-5.69935	3
		LEU 727	H	O	2.09		
		ASN 176	O	H	1.94		
Chemokine receptor, 4MBS	6-(4-Chlorophenyl)-3-cyano-4-(N-benzylpiperazino)-2H-pyran-2-one	THR 195	H	O	2.32	-8.423	1
FGF receptor, 1PWA	Pyrrolidine, 1-methyl-2-phenyl-3-(phenylsulfonyl)	SER 144	O	H	2.22	-4.081	3
		CYS 70	H	O	1.81		
		LEU 145	O	H	2.26		
Melatonin receptor, 4GR9	Pyrrolidine, 1-methyl-2-phenyl-3-(phenylsulfonyl)	LYS 113	H	O	2.38	-4.861	2
		GLY 174	O	H	1.76		
Estrogen receptor, 1A52	2-(4-Aminophenyl)-5-hexynoic acid	GLU 353	O	H	1.88	-5.946	1
Adrenergic receptor, 2RH1	5-Imino-7-phenyl-2,3-dihydro-5H-thiazolo[3,2-1] pyrimidine-6-carbonitrile	ILE 135	C	N	2.2	-6.326	0
		TRY 326	C	H	4.05		
		ILE 58	C	H	7.47		

Table 3: Interaction profile of bioactive phytoconstituents from synthesized nanoparticles from aqueous extract of fresh leaf of *G. polycaulon*.

Proteins	Protein Complex	Amino Acid	Protein Atom	Ligand Atom	Bond Length	G Score	No of Hydrogen Bonds
Toll-like receptor, 2J67	2-Benzyl-3-(4-methoxyphenyl)-6-chloro-7,8-dihydroisoquinolin-1(2H)-one	GLU 659	O	H	1.64	-5.203	1
Chemokine receptor, 4MBS	4,5-Bis(p-bromophenoxy)-1,2-dicyanobenzene	LEU 221	O	H	1.96	-7.436	3
		GLU 1054	O	H	1.68		
		GLU 1051	O	H	1.73		
FGF receptor, 1PWA	4-methoxycarbonylmethylthio-1-triisopropylsilylindole	LEU 145	O	H	2.33	-4.455	2
		LEU 145	O	H	1.86		
Melatonin receptor, 4GR9	9,10-Anthracenedione	LYS 117	H	O	2.08	-3.254	1
Adrenergic receptor, 2RH1	4,5-Bis(p-bromophenoxy)-1,2-dicyanobenzene.	ASP 331	O	H	1.74	-5.591	3
		ASP 331	O	H	1.7		
		ARG 63	O	H	1.64		

Table 4: Interaction profile of bioactive phytoconstituents from methanolic extract of dried leaf of *G. polycaulon*.

Protein	Protein Complex	Amino Acid	Protein Atom	Ligand Atom	Bond Length	G Score	No of Hydrogen Bonds
Toll-like receptor, 2J67	6-[2-(3-Hydroxy-4-methoxyphenyl)ethyl]-4-methoxy-5,6-dihydro-2H-pyran-2-one	LYS 751	H	O	2.02	-5.062	2
		LEU 272	O	H	2.09		
Chemokine receptor, 4MBS	2-Pentyne-1,4-diol, 4-methyl-1-(2-thienyl)	GLU 283	O	H	1.95	-5.115	1
Melatonin receptor, 4GR9	6-[2-(3-Hydroxy-4-methoxyphenyl)ethyl]-4-methoxy-5,6-dihydro-2H-pyran-2-one	ASP 117	O	H	2.05	-3.823	1
Estrogen receptor, 1A52	2,6,10,15,19,23-Hexamethyl-2,6,14,18,22-tetracosapentaene-10,11-diol	TYR 526	H	O	1.94	-2.527	1
Adrenergic receptor, 2RH1	6-[2-(3-Hydroxy-4-methoxyphenyl)ethyl]-4-methoxy-5,6-dihydro-2H-pyran-2-one	ARG 31	H	O	2.21	-5.543	1

Table 5: Interaction profile of bioactive phytoconstituents from synthesized nanoparticles from methanolic extract of dried leaf of *G. polycaulon*.

Proteins	Protein Complex	Amino Acid	Protein Atom	Ligand Atom	Bond Length	G Score	No of Hydrogen Bonds
Toll-like receptor, 2J67	Dihydrokhusilal acid	LYS 691	H	O	2.13	-4.847	3
		LYS 691	H	O	1.87		
		HIE 724	H	O	2.19		
Chemokine receptor, 4MBS	4-Chloro-4-methylpentane-2,3-dione	ASH 76	H	O	1.86	-6.601	1
FGF receptor, 1PWA	Methanesulphinic acid methyl ester	MET 109	H	O	2.2	-2.884	1
Melatonin receptor, 4GR9	Dihydrokuhusilal acid	LYS 113	H	O	1.83	-4.566	1
Estrogen receptor, 1A52	Methane, sulfinylbis	LYS 449	H	O	1.99	-4.543	1
Adrenergic receptor, 2RH1	6-Methyl-2-(4-nitrophenyl)-5-phenylthio-2,3-dihydro-4-pyrone	ASN 69	H	O	1.89	-5.878	1

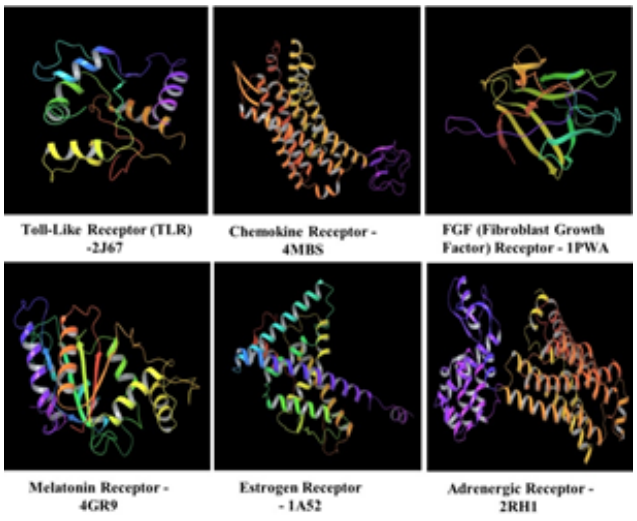

Figure 1: Protein with structure and ID from protein data bank present in *G. polycaulon*.

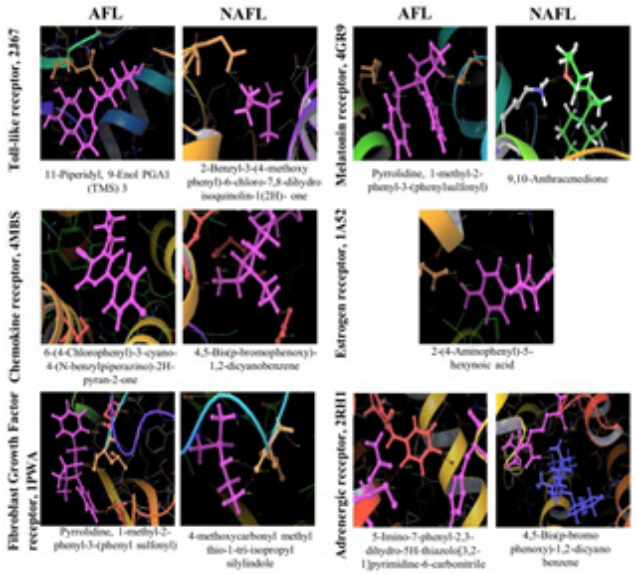

Figure 2: Interaction profile of bioactive phytoconstituents from aqueous extract of the fresh leaf (AFL) and synthesized nanoparticles from aqueous extract of the fresh leaf (NAFL) with the receptor.

phytocompounds act as ligands to determine the efficiency to bind with six different protein receptors, which have wound healing potential.[27,28,40] This can be possible by using the molecular docking process in the plant source for wound care management.[34,37] It was observed that functional groups of selected proteins could bound with specific compounds. This confirms the selected compounds act as an effective would heal potential.[12,22,29] This could be confirmed the toxicity by any of the open-source software, such as the QikProp module from Schrodinger.

G. polycaulon extracts showed greater interaction with six target protein receptors with binding energy, which has

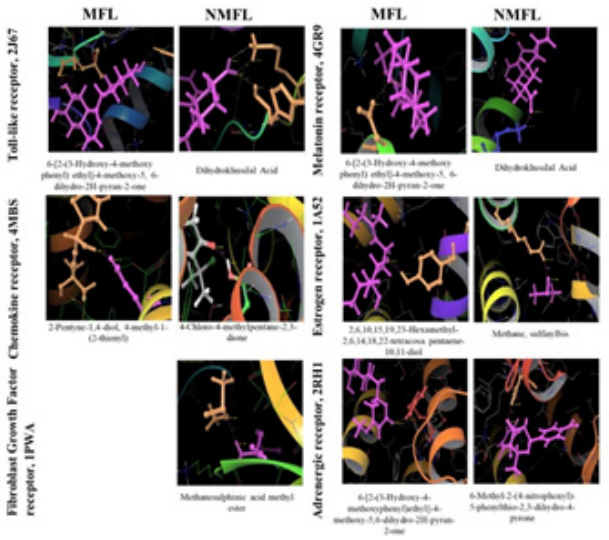

Figure 3: Interaction profile of bioactive phytoconstituents from methanolic extract of the dried leaf (MFL) and synthesized nanoparticles from methanolic extract of the dried leaf (NMFL) with the receptor.

been confirmed by the Glide score range. The previous studies reported that the selected phytoconstituents should have high binding energy along with respective Glide score range, which will result in effective pharmacological activity.[28,30] The results confirmed that all the selected phytocompounds were possessed significant wound healing potential. Therefore, the selected phytocompounds could be effectively used for wound healing, anti-inflammatory, anti-diabetic and antioxidant activities.

CONCLUSION

Greater interaction with target proteins has been observed for 2J67, 4MBS, 1PWA, 4GR9, 1A52 and 2RH1 was docked with ligand from GC-MS compounds of four selected test extracts. Silver nanoparticles has been observed as highly stable and stored for a longer period. It was also confirmed that a very minimum amount is required to treat the ailment. In addition, the present study was the first report about the pharmacological activity of the *G. polycaulon* plant in the southern part of India. This plant possesses much beneficial ability due to the presence of bioactive phytocompounds, which should be documented in an elaborated manner. In conclusion, the present investigation provides detailed information, habitat and evidence about various applications of the plant *G. polycaulon*.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

G. polycaulon: *Gnaphalium polycaulon;* **GC MS:** Gas chromatography-mass spectrometry; **mM:** Millimolar; **°C:** Degree Centigrade; **HTS:** High-throughput screening; **PDB:** Protein Data Bank; **3D:** Three Dimension.

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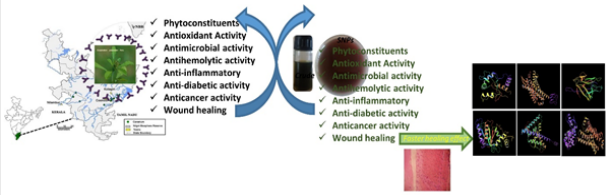
PICTORIAL ABSTRACT



SUMMARY

G. polycaulon has significant biological potential related to wound healing. The more specific phytocompounds were identified by GC-MS analysis. Wound healing related protein was docking with ligands from *G. polycaulon* extracts. *In silico* analysis was performed for the confirmation of phytocompounds.

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