Biological Forum – An International Journal **15(5): 104-113(2023)**

ISSN No. (Print): 0975-1130
ISSN No. (Online): 2249-3239

Wound Healing Potential of Bioactive Compound from *Cayratia trifolia* (L.): An *In silico* and *In Vitro* analysis

Bhuvaneswari Meganathan and Mani Panagal*

Department of Biotechnology, Annai College of Arts and Science (Affiliated by Bharathidasan University), Kovilacheri, Kumbakonam (Tamil Nadu) 612503, India.

(Corresponding author: Mani Panagal)*
(Received: 20 March 2023; Revised: 24 April 2023; Accepted: 02 May 2023; Published: 20 May 2023)
(Published by Research Trend, Website: www.researchtrend.net)

ABSTRACT: The process of wound healing involves replacing damaged cellular structures with functional ones. Wounds have been treated with medicinal plants and their active compounds for thousands of years. Chinese and Indian traditional medicines have proven effective in healing. Medicinal plant of *Cayratia trifolia* L (*C. trifolia*) has variety of phytocompounds and they extracts possess antiviral, antibacterial, antiprotozoal, hypoglycemic, anticancer, and wound healing properties. Therefore, in this study ethanolic extract of *C. trifolia* was investigated to determine its bioactivity, structure, and wound healing capability of bioactive compound. Initially, linolenyl alcohol (cmd-1) was identified by chromatographic and spectroscopic methods. Even at highest concentrations of 200 µg/ml in normal fibroblasts cell lines of Normal Human Dermal Fibroblasts cells (NHDF) and Human Umbilical Vein Endothelial cells (HUVEC), it does not appear to be cytotoxic. Molecular docking studies revealed that, when compared with reference drug, cmd-1 have strong binding affinity with wound healing related target proteins such as PKC βII (Protein kinase C βII), TNF-α (Tumor necrosis factor alpha), IL-1β (Interleukin-1 beta), PDGFRA (Platelet-derived growth factor receptor alpha), VEGF-A (Vascular endothelial growth factor A) and TGFBR1 (Transforming Growth Factor Beta Receptor 1) and docking score ranges from -3.8 to -7.1 Kcal/mol. These compounds exhibited acceptable ADME properties. As a result of this study, it can be concluded that the isolated bioactive compound of linolenyl alcohol may be able to heal wounds. Experiments *in vitro* and *in vivo* are needed to confirm these findings.

Keywords: *Cayratia trifolia* L., linolenyl alcohol, Molecular docking, Wound healing.

INTRODUCTION

In addition to maintaining the body's homeostasis, the skin protects the body from pathogenic microbes, UV rays, toxins, and other effects of environmental factors (Pei *et al.,* 2023). It is normal for wounds to heal within three months after disturbances to the skin integrity. Chronic wounds are wounds that do not heal within three months and may result from a variety of causes. A chronic wound is one of the silent killers of the aging population, which poses many risks to them (Xu *et al.,* 2020). People suffering from a variety of life style disorders, such as diabetes, nephropathies, cardiovascular disease, etc., are also susceptible to chronic wounds that do not heal properly. Individuals who suffer from chronic wounds are negatively affected by their productivity, as well as the country as a whole, as a chronic wound has a significant economic impact (Pei *et al.,* 2022). It has been reported that chronic wounds have accounted for 70 percent of limb amputations in diabetic patients, and overall 85% of ulcers have resulted in limb amputations. It is estimated that 40–70% of patients who have undergone major amputations will die within 5 years (Prasad *et al.,* 2022). It is important to note that microbial infections are a major factor in wounds that do not heal. In addition to inhibiting microbe colonization, many of the drugs available on the market are intended to enhance wound healing capacity (Palanisamy *et al.,* 2022).

Cetrimide solution, sodium hypochloride, chlorhexidine, etc. are the most commonly used medications in developing countries to treat wounds (Adeniran *et al.,* 2023). These medications, however, have been shown to be ineffective and can also result in side effects when prolonged (Prasad *et al.,* 2022). Furthermore, polypeptide growth factors are the major constituents of many wound-healing medicines of today, which stimulate and control the proliferation of cells at the wound site (Jayaraman *et al.,* 2021). It is possible, however, that the proliferation-inducing properties of these growth factors may also contribute to the development of cancer (Sowmya *et al.,* 2021).

Traditional herbal medicine practitioners have described the therapeutic effects of a number of indigenous plants for a variety of diseases (Pei *et al.,* 2022; Jayaraj *et al.,* 2022; Palanisamy *et al.,* 2021; Palanisamy *et al.,* 2023). Synthetic and traditional herbal medicines can be derived from natural products (Palanisamy *et al.,* 2021). Some parts of the world still rely on them as their primary health care system (Vidya *et al.,* 2016). Within the past decade, the perception of ethnopharmacological therapeutic applications has changed considerably. It has

been observed that a variety of life-sustaining constituents are present in plants, which has led scientists to study those plants with the aim of determining their potential for healing wounds (Priyanga *et al.*, 2017; Kumatr *et al.*, 2016; Malarvizhi *et al.*, 2015; Starlin *et al.*, 2012). *Cayratia trifolia* (L.) (*C. trifolia*) belongs to the family of Vitaceae and is used as a medicinal plant (Fig. 1).

Fig. 1. Medicinal plant of *Cayratia trifolia* (L.).

Fox grapes are commonly used as a name for this plant, which is native to India, Asia, and Australia (Meganathan *et al.*, 2021; (Perumal *et al.*, 2015). Based on preliminary phytochemical screening, the whole *C. trifolia* plant contains yellow waxy oil, steroids, terpenoids, flavonoids, and tannins. Several studies reported that, the leaves of *C. trifolia* contain stilbenes, piceid, reveratrol, viniferin, and ampelopsin, as well as stilbenes (Perumal *et al.*, 2016; Perumal *et al.*, 2015). In addition to hydrocyanic acid, delphinidin is also reported to be present in the stem, leaves, and roots (Sowmya *et al.*, 2015). It has been reported that the leaves contain several flavonoids, such as cyanidins. It is possible to prepare a decoction of roots by mixing them with coconut oil. As a poultice on boils, ground roots can be combined with black pepper (Perumal *et al.*, 2015). Traditionally, diabetic patients are given an oral infusion of seeds along with an extract of tubers to monitor their blood sugar levels (Sowmya *et al.*, 2015). During the treatment of snake bites, a paste made from tubers is applied to the affected area (Perumal *et al.*, 2014). In tumors, neuralgia, and splenopathy, the whole plant is regarded as a diuretic (Sowmya *et al.*, 2014). Studies conducted with animal models have shown that the bark extract has antiviral, antibacterial, antiprotozoal, hypoglycemic, anticancer, and diuretic properties (Perumal *et al.*, 2012). Therefore, the aim of the present study is to isolate the bioactive compound from ethanolic extract of *C. trifolia* and to validate their wound healing activity by *in silico* and *in vitro* molecular analysis.

MATERIAL AND METHODS

A. Plant collection

In the area of Kumbakonam, Thanjavur District, Tamil Nadu, India, the whole plant of *C. trifolia* was collected and washed the plant material under running tap water, allowed it to dry naturally, then powdered it for further examination.

B. Extract preparation

We extracted 600 g of plant powder with 3000 ml of ethanol over 72 hours at room temperature in an occasional shaker. Under reduced pressure, an evaporator was used to collect the extract and concentrate it at 40°C. Until further compound isolation, the dried extract was stored at 4°C (Palanisamy *et al.*, 2022).

C. Compound isolation

A thin layer chromatography (TLC) technique was used to isolate the compounds. Leaf extracts containing ethanol were used to separate the elements. Following fractionation of 15 g of the extract on a TLC silica gel column, elution is accomplished by using petroleum ether (3 × 30 cm), petroleum ether: chloroform (8:2, 6:4, 4:4, 2:8 v/v) and chloroform (100%) respectively. To confirm the presence of saturated fractions, the fractions are gathered in a 20 ml test tube and analyzed individually using TLC plates (Palanisamy *et al.*, 2020).

D. Structural characterization

It is determined that the presence of a functional group is present in a secluded compound using a Fourier Transform Infrared Spectrometer with a resolution of 0.1/cm. A Perklin Elmer polarimeter (model 341) was used to measure the optical activity of compounds using the Polarimetry technique. As a preliminary step in determining the purity of the sample, NMR spectra were recorded on the CDC13 solutions using a Burker DRX-500 NMR spectrometer at 500 MHz, and the signals were used as a reference (Palanisamy *et al.*, 2019).

E. In silico analysis

Selection and preparation of ligands. The isolated bioactive compound and the FDA-approved drug (nitrofurazone) were prepared using PyRx software with default parameters, followed by energy minimization using universal force fields, followed by Gasteiger charges in order to achieve a good structural conformity for docking with PyRx software with default parameters (Palanisamy *et al.*, 2018).

Selection and preparation of receptors. In order to conduct this study, six different proteins involved in wound healing were selected, and their crystal structures were obtained from the Protein Data Bank (PDB). Any missing residues in the selected target proteins were modeled in Chimera 1.16, nonstandard heteroatoms were removed, polar hydrogens were added, and Gasteiger charges were added to the model. A steepest descent gradient method of energy minimization was followed for each protein using an Amber force field (Amber ff14SB). In order to convert the energy minimized protein, the pdbqt format was used for molecular docking (Anusooriya *et al.*, 2015).

Protein-ligand docking. We utilized Autodock Vina for molecular docking of cmd-1 with selected wound healing target proteins. A ligand binding site will be displayed in the center of the grid box if it is represented. It is determined that the model is exhaustive by setting a value of eight. In accordance with the dimensions of the XYZ axis determined by Discovery studio's visualizer, a configuration file was created. A configuration file used for docking using the command line was included in

Autodock Vina 1.1.2. The Monte Carlo algorithm is used to dock ligands with a degree of flexibility. In comparison to other docking programs, Autodock Vina uses a Monte Carlo algorithm. Furthermore, the binding modes were generated as a single file (PDBQT format) in a log format, in addition to the results file. An analysis of the binding interactions between the best docked ligands and receptors was carried out using the BIOVIA Discovery Studio visualization. A hydrogen bond between two heavy atoms was measured as strong (2.2 to 2.5), moderate (2.5 to 3.2), and weak (up to 3.6) (Kannayiram *et al.*, 2022).

ADME properties prediction. In order to predict ADME properties, we used the QikProp module (Schrodinger Suite 2022). QikProp analyzes ligand properties similar to those of drugs in order to determine the ligand's pharmacokinetics and pharmacodynamics. The logarithm of the n-octanol/water partition coefficient and molecular weight (MW) were considered to be important ADME properties (Palanisamy *et al.*, 2019).

F. In vitro cytotoxicity analysis

Cell line and culture. A cell line of HUVECs and a cell line of NHDFs were obtained from NCCS Pune, India for the purpose of this study. During the experiment, 37°C was maintained in a humidified atmosphere containing 5% CO_2. Growing the cells in T-25 flasks was accomplished using DMEM medium supplemented with 10% FBS and 1% antibiotics (100 U/ml penicillin and 100µg/mL streptomycin). Upon reaching confluence, the cells were trypsinized and passaged.

Cell viability analysis. cmd-1 stock solutions were diluted in DMSO to a concentration of 10 mg/mL in culture media. The viability of cells was determined by seeding 5×10^3 cells into 96-well plates and incubating them at 37°C and 5% CO_2 for 24 hours. Incubation was conducted for 24 hours in DMEM medium supplemented with various concentrations of cmd-1 (0, 10, 20, 50, 100 mL). To determine the viability of the cells, they were incubated for two hours in growth media containing 20% MTS solution after being incubated with cmd-1. For the measurement of 490 nm absorbance of formazan, microplate readers were used. As the vehicle culture medium contained a high concentration of DMSO, cmd-1 was dissolved in 0.5% DMSO (Palanisamy *et al.*, 2021).

G. Statistical analysis

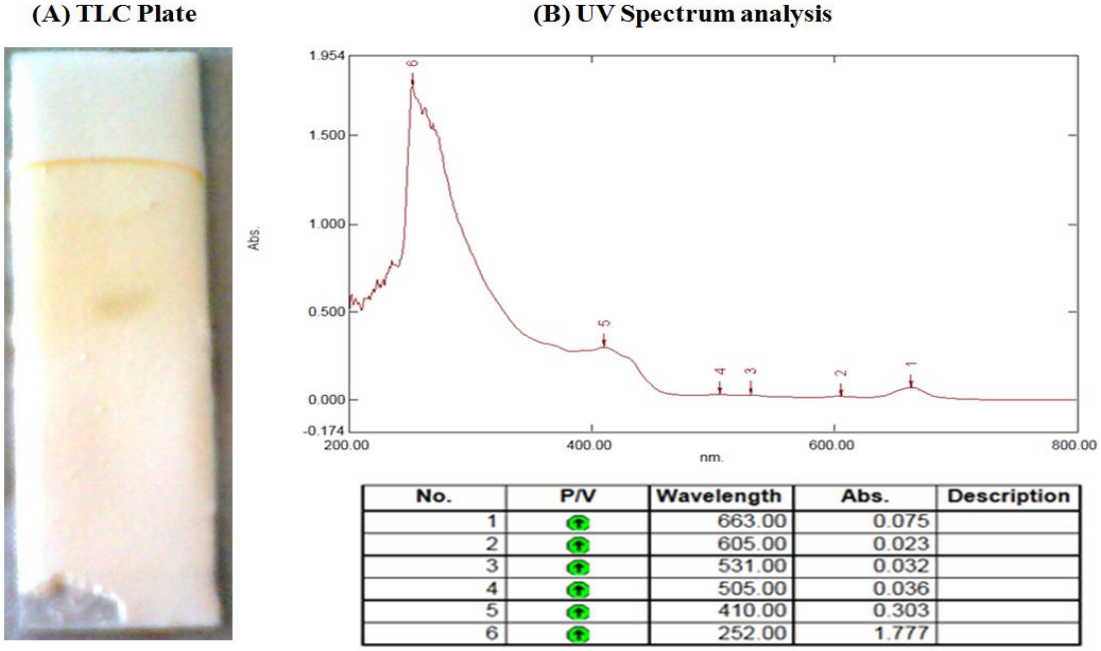
In order to determine the significance of individual differences between the control and treatment groups, one-way analysis of variance (ANOVA) and Duncan's multiple range test were performed using GraphPad Prism version 5 software. In Duncan's test, P=0.05 was considered significant (Manimaran *et al.*, 2022).

RESULTS AND DISCUSSION

A. Compound isolation and structural characterization

Chemical separation of compound mixtures is achieved through column chromatography. Preparative applications involving micrograms to kilograms are often carried out with this product. There are several advantages to this process, including relatively low cost and disposability of the stationary phase. As a result of recycling, the stationary phase is protected from cross-contamination and degradation (Poornima *et al.*, 2017; (Ragavendran *et al.*, 2012).

A total of 273 fractions were obtained from the column chromatography by sequential solvent elevation from a low polar to a highly polar solvent. The single compound was identified from fraction number 222-236 with the Rf value 0.7 cm using TLC analysis (Fig. 2) and it may indicate the presence of a single compound in this fraction. About 450 mg of the pure compound was obtained from the single fraction and it was used for further studies. The UV-Visible spectroscopy analysis showed the major absorption bands at °max of 252nm and at maximum absorbance is 1.777 which also indicates the presence of single compound.



No.	P/V	Wavelength	Abs.	Description
1		663.00	0.075	
2		605.00	0.023	
3		531.00	0.032	
4		505.00	0.036	
5		410.00	0.303	
6		252.00	1.777	

Fig. 2. (A) Single compound identification by TLC analysis and (B) °max analysis for cmd-1 through UV spectrum.

In the FTIR spectrum (Fig. 3) showed and functional group characteristic absorption band at 1728 cm^{-1} for a carbonyl group and a shoulder peak at 2858 cm^{-1} for an aldehyde hydrogen group (CHO). The bands at 2924 cm^{-1} is due to C-H stretching and the bands at 1458 and 1381 cm^{-1} are due to C-H bending bonds. The band at 1529 cm^{-1} may be due to the C=C group.

In the 1H-NMR spectrum (Fig. 4) the triplet at δ 0.836 indicates the presence of a methyl group, the strong singlet at δ 1.25 is due to the presence of long chain methylene protons. The signal at δ 2.27 is due to the methylene group adjacent to a carbonyl group. The presence of signals at δ 1.41 and 2.02 indicates the presence of methylene group adjacent to a C=C. The multiplet at δ 4.94 is due to the presence of unsaturated protons. The mass spectrum indicates the presence of two double bonds. The presence of peaks at m/z 222, 151, 83, 97 represents the double bonds at C8 and C13. From all the above spectral studies the cmd-1 was characterized and the assumed structure of the compound as linolenyl alcohol, its molecular weight 264.44 g/mol and molecular formula is $C_{18}H_{22}O$ (Fig. 5).

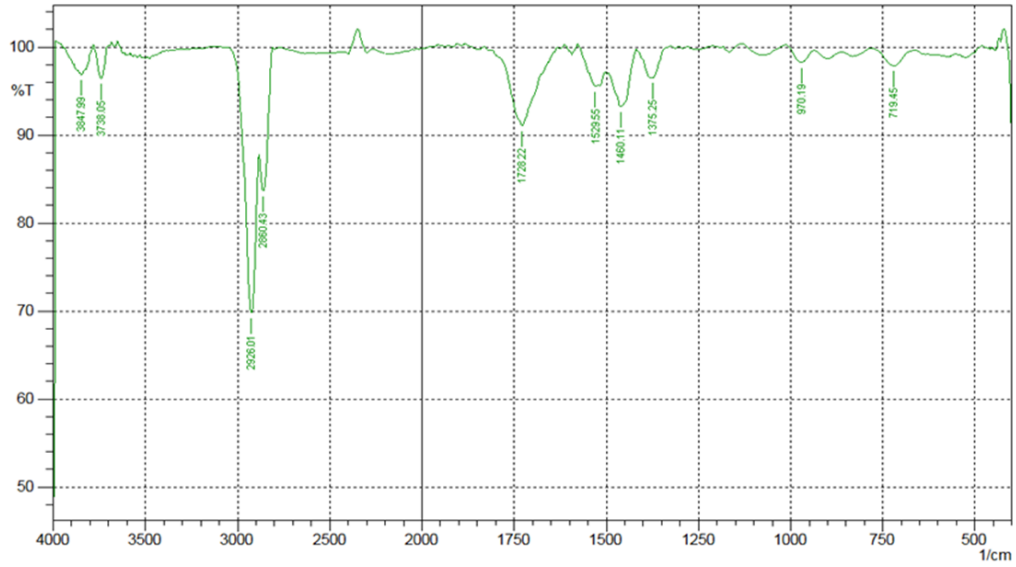


Fig. 3. FTIR spectrum for cmd-1 which indicates presence of functional groups by the characteristic absorptions (1/cm).

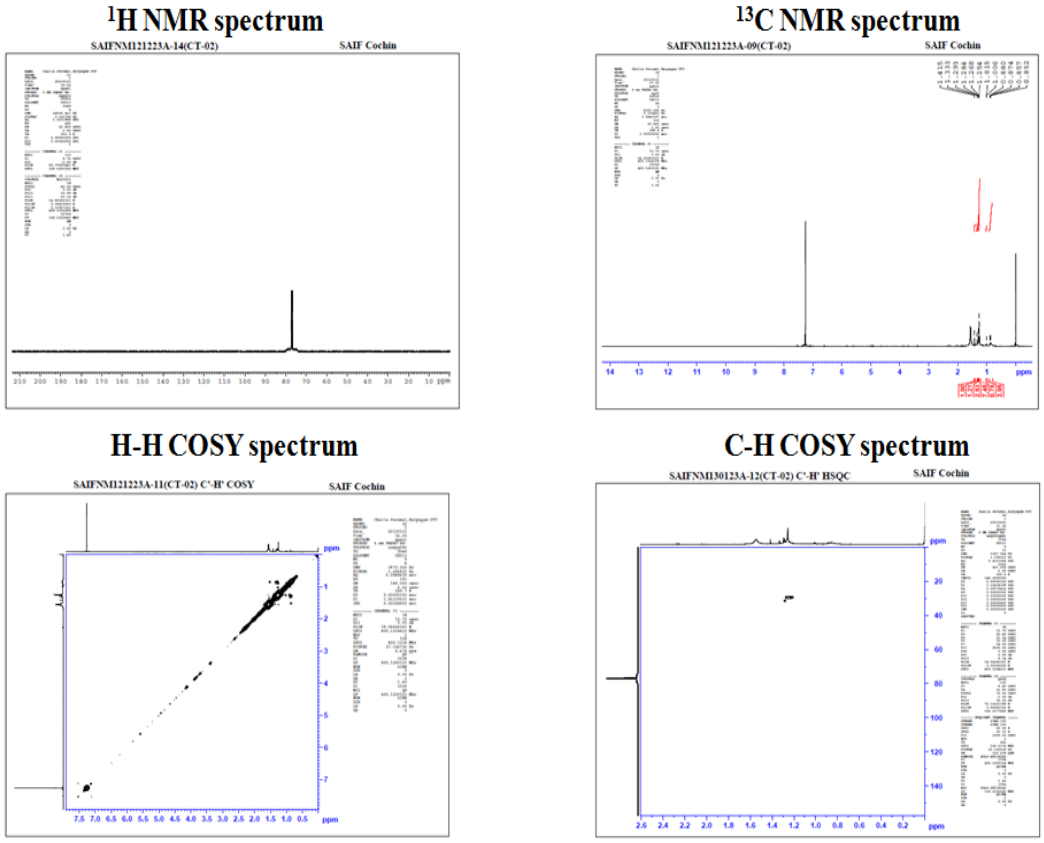


Fig. 4. NMR spectrum analysis of cmd-1.

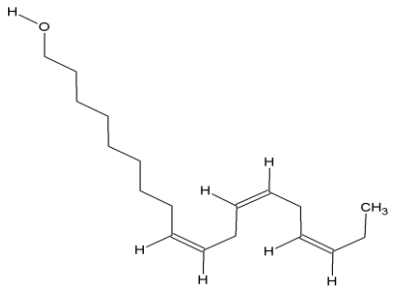


Fig. 5. The structure of isolated and identified bioactive compound of Linolenyl Alcohol (cmd-1).

B. Effect of cmd-1 on cell viability of NHDF and HUVEC cells

Two different fibroblast cell lines were used in order to test the cytotoxicity of the isolated bioactive compound (NHDF and HUVEC cells) at different concentrations of cmd-1. Fig. 6 shows that the highest concentration of cmd-1, 200 µg/ml, did not exhibit cytotoxicity against fibroblast cell lines when plotted against its treatment concentrations.

C. Computational analysis

In the present study, we have used Autodock vina for predicting the binding affinity of cmd-1 and standard drug (nitrofurazone) with the target proteins of wound healing process such as TNFα (PDB ID: 2AZ5), TGFBR1 kinase (PDB ID: 6B8Y), IL-1β (PDB ID: 6Y8M), PKC-βII (PDB ID: 2I0E), VEGF-A (3QTK) and PDGFRA (PDB ID: 6JOL). Based on Fig. 7-12 and Table 1, it is evident that the isolated bioactive compound of linolenyl alcohol demonstrated comparable binding affinity to all target proteins tested. ADME properties of isolated compound and reference drug were under acceptable range (Table 2).

Wounds causing inflammation are caused by high levels of tumor necrosis factor alpha (TNFα). Evidence suggests that inhibition of TNFα is a critical for treatment of wounds (Palanisamy *et al.*, 2023). The growth factor TGFβ plays an important role in wound healing due to its benefits for reepithelialization, inflammation, angiogenesis, and new tissue growth (Ruder *et al.*, 2019). In order to predict the potential therapeutic effects of phytocompounds of cmd-1 against wound healing-related molecular targets, we have performed docking studies with TNFα, TGFBR1 kinase, IL-1β, PKC-βII, VEGF and PDGF. We predicted that an isolated bioactive compound of cmd-1 from ethanolic extract of *C. trifolia* would show strong binding affinity to selected wound healing targets based on docking studies.

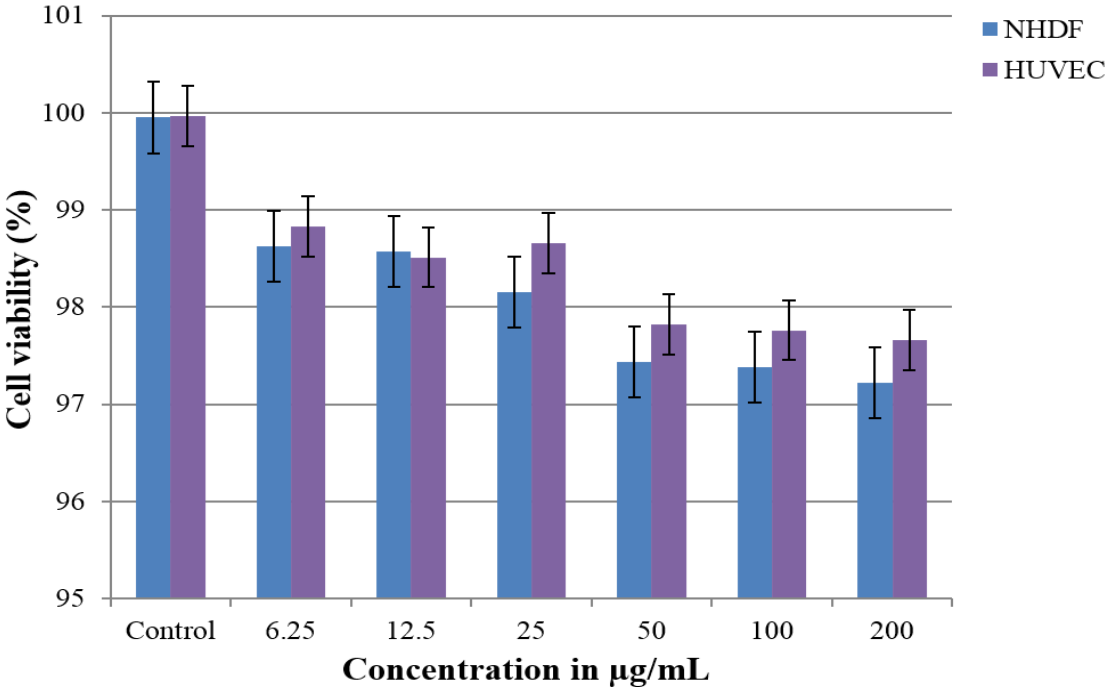


Fig. 6. Effect of cmd-1 on cell viability of NHDF and HUVEC cells.

Table 1: Docking analysis of cmd-1 and standard drug with wound healing target proteins.

Sr. No.	Target Proteins (PDB ID)	Cmd-1 (kcal/mol)	Standard Drug (kcal/mol)
1.	TNFα (2AZ5),	-5.6	-5.8
2.	TGFBR1 kinase (6B8Y),	-6.3	-6.2
3.	IL-1β (6Y8M),	-3.8	-4.0
4.	PKC-βII (PDB: 2I0E),	-5.8	-5.9
5.	VEGF-A (3QTK)	-4.4	-4.6
6.	PDGFRA (6JOL).	-7.1	-6.9

Table 2: ADME properties prediction of isolated compound and reference drug.

Compound name	Mol. Wt.	H. Bond Donor	H. Bond Acceptor	Log P	Rotatable Bond
cmd-1	264.4	1	1	4.9	13
Standard Drug	198.1	2	5	0.2	2

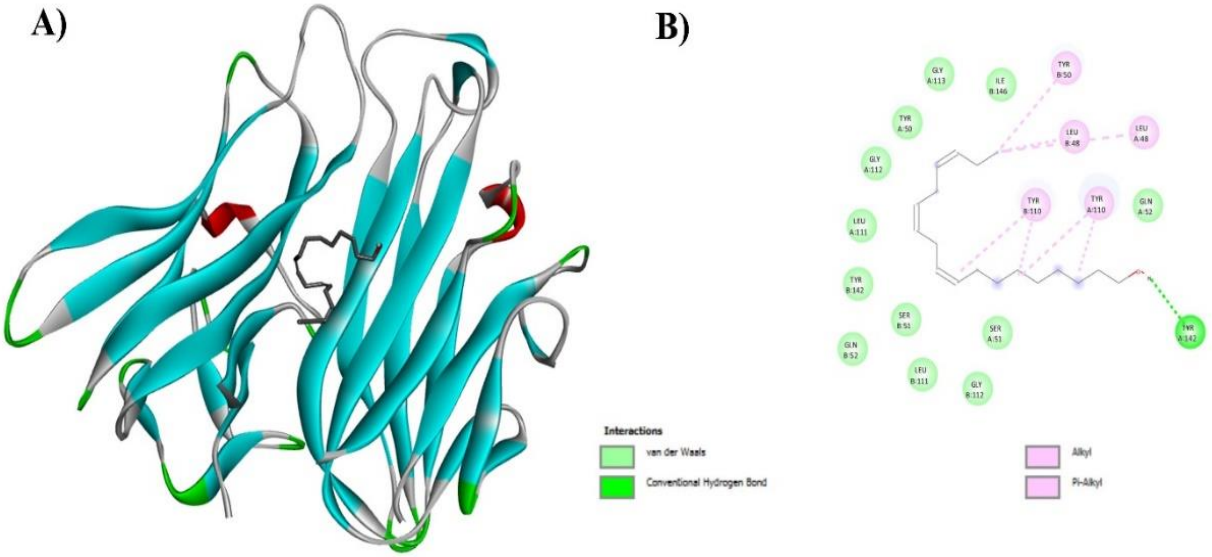


Fig. 7. Docking analysis of cmd-1 complexed with TNFα. A) 3D structure of docked complex and B) 2D structure of docked complex.

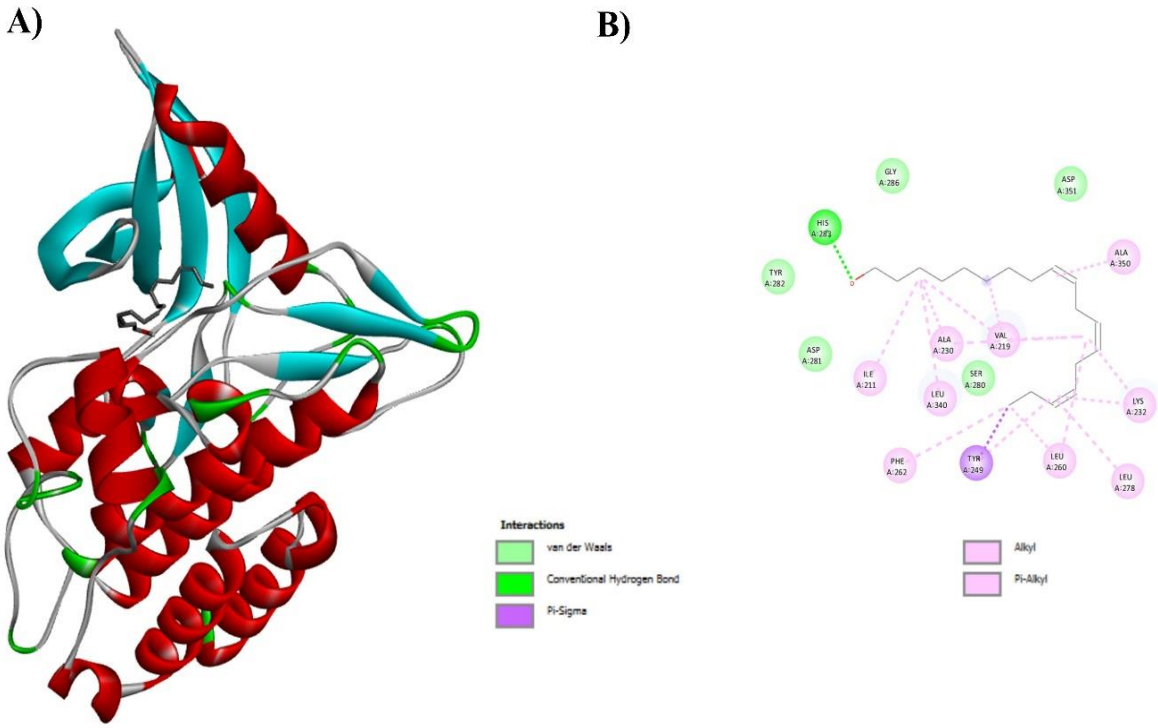


Fig. 8. Docking analysis of cmd-1 complexed with TGFBR1 kinase. A) 3D structure of docked complex and B) 2D structure of docked complex.

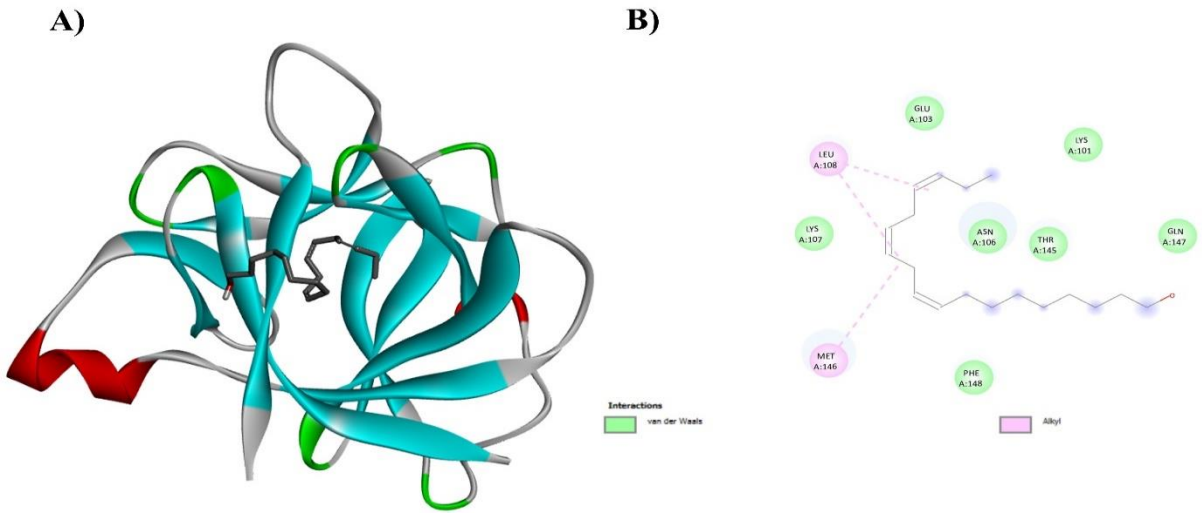


Fig. 9. Docking analysis of cmd-1 complexed with IL-1β. A) 3D structure of docked complex and B) 2D structure of docked complex.

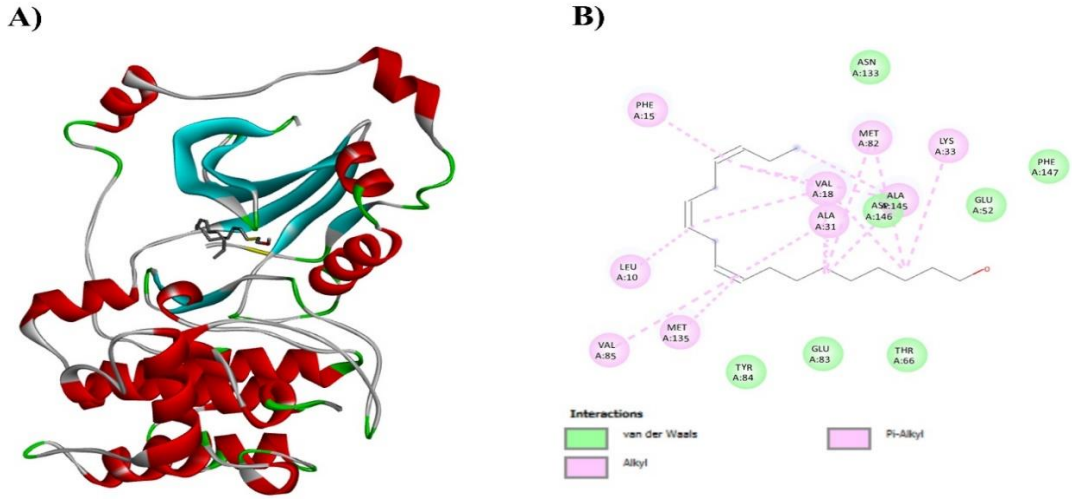


Fig. 10. Docking analysis of cmd-1 complexed with PKC-βII. A) 3D structure of docked complex and B) 2D structure of docked complex.

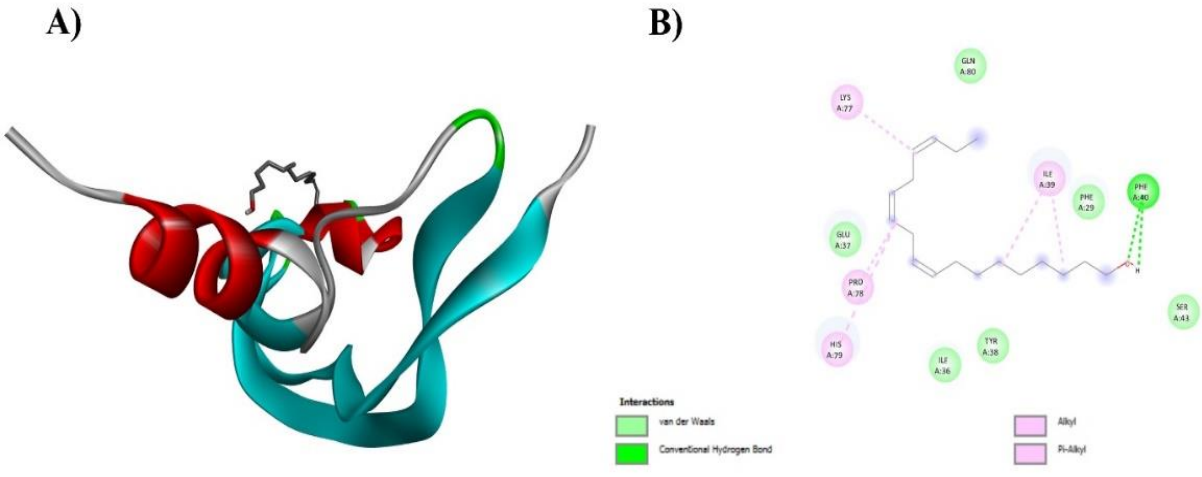


Fig. 11. Docking analysis of cmd-1 complexed with VEGF-A. A) 3D structure of docked complex and B) 2D structure of docked complex.

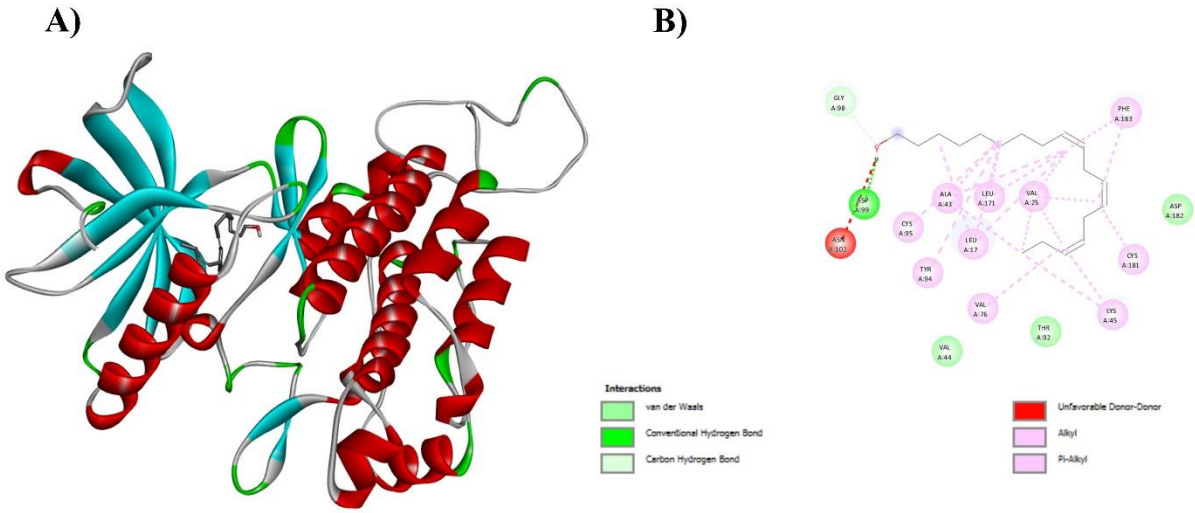


Fig. 12. Docking analysis of cmd-1 complexed with PDGFRA. A) 3D structure of docked complex and B) 2D structure of docked complex.

CONCLUSION

Linolenyl alcohol was isolated and identified by chromatographic and spectroscopic methods from ethanolic extracts of *C. trifolia*. NHDF and HUVEC fibroblast cell lines were not cytotoxic by cmd-1 at highest concentrations of 200 µg/mL in *in vitro* cytotoxicity analysis. A computational docking study associated with cmd-1 also observed that it was able to interact well with wound healing targets PDGFRA, VEGF-A, and TGFBR1 kinase with docking scores ranging from -3.8 to -7.1 Kcal/mol. Those compounds showed acceptable ADME properties. This study concludes that linolenyl alcohol isolated from ethanolic extract of *C. trifolia* may have wound healing properties based on its *in vitro* and *in silico* results. For the current funding to be confirmed, further analysis of *in vitro* and *in vivo* experimental animal models is needed.

FUTURE SCOPE

Several *in vitro* and *in silico* studies have shown that linolenyl alcohol taken from an ethanolic extract of *C. trifolia* has wound healing properties. There is a possibility that it will lead to the development of new drug candidates for a system of disease management for humans in the future.

Acknowledgement. We authors are expressing our sincere thanks to Department of Biotechnology, Annai College of Arts and Science, Kumbakonam, Tamil Nadu, India for the completion of this research work in fine fulfillment.

Conflict of Interest. Authors have declared that no competing interests exist.

Author contributions. Bhuvaneswari Meganathan and Mani Panagal: Conceived and designed the analysis; Collected the data; Contributed data or analysis tools; Performed the analysis; Wrote the paper.

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How to cite this article: Bhuvaneswari Meganathan and Mani Panagal (2023). Wound Healing Potential of Bioactive Compound from *Cayratia trifolia* (L.): An in silico and in vitro analysis. *Biological Forum – An International Journal, 15*(5): 104-113.