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Bioactive Compound from *Mollugo nudicaulis* Lam. Promotes Wound Healing Activity: An *In Silico* and *In Vitro* Analysis

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ABSTRACT: Cells are replaced with functional ones during wound healing. Medicinal plants and their active compounds have been used for thousands of years to treat wounds. It has been proven that Chinese and Indian traditional medicines are effective in wound healing. There are many phytocompounds in *Mollugo nudicaulis* Lam. (*M. nudicaulis*) and their extracts are possessing antiviral, antibacterial, antiprotozoal, hypoglycemic, anticancer, and wound-healing activities. Therefore, the present study aims to identify and isolate a bioactive compound with wound healing properties. As a first step, ethanolic extract of *M. nudicaulis* was subjected to chromatographic and spectroscopic analyses in order to determine the bioactive compound. The wound healing activity of isolated compound with targeted proteins (such as PKC βII, TNF-α, IL-1β, PDGFRA, VEGF-A and TGFBR1) was investigated using computational molecular analysis. Furthermore, normal fibroblast cell lines were used to assess cytotoxicity. Based on the results of the TLC, FT-IR, ^{13}C and ^{1}H NMR analyses, the isolated compound was identified as 12-(10-carboxydecanoyloxy)-12-oxododecanoic acid (cmd-1). Cmd-1 binding affinity for wound healing target proteins is comparable to that of nitrofurazone (a drug approved by FDA), and docking scores range from -4.0 to -6.9 kcal/mol. Neither isolated compound nor standard drug displayed undesirable ADME properties. It has been shown that cmd-1 is not cytotoxic to NHDF and HUVEC cells, even at high concentrations of 200 µg/mL. Accordingly, ethanolic extract of *M. nudicaulis* provides a bioactive compound that may function as a novel wound healing agent and, potentially, lead to the development of novel therapeutic agents. However, *in vitro* and *in vivo* experiments will be necessary to confirm the current findings.

Keywords: *Mollugo nudicaulis* Lam., 12-(10-carboxydecanoyloxy)-12-oxododecanoic acid, Molecular docking, Wound healing.

INTRODUCTION

There is a growing demand for specialized wound care services around the world due to wounds being a significant medical problem (Pei *et al.*, 2023). Wounds are classified based on their pathophysiology, *viz*., acute wounds, chronic wounds, and burns wounds. Inflammation, proliferation, and maturation are three phases of wound healing. According to the mechanism of injury and the size of the lesion, acute wounds usually recover completely within 5 to 10-days (Xu *et al.*, 2020). There is a failure of one or more healing phases in chronic wounds, causing them to take longer than expected to heal, usually over four weeks. The pathophysiology and natural course of burn wounds differ from those of other cutaneous wounds, so they are accounted for as a separate group. There are three zones of burn wounds (Pei *et al.*, 2022). Usually, the coagulation zone consists of necrosis that is located centrally. In the absence of other attacks, the hyperemic zone will recover. Last, the zone of stasis situated between the coagulation and hyperaemia zones will progress in accordance with the rate of perfusion during the first few days following the injury (Prasad *et al.*, 2022). If the stasis zone progresses to necrosis, it may lead to wound deepening and widening (Palanisamy *et al.*, 2022).

The use of synthetic drugs for the treatment of diabetic wounds is common, but they have a number of significant limitations (Adeniran *et al.*, 2021; Perumal *et al.*, 2014; Perumal *et al.*, 2012; Prasad *et al.*, 2022). It has been proven that the active ingredients in medicinal plants are safe agents for treating wounds (Sowmya *et al.*, 2014; Perumal *et al.*, 2015; Jayaraman *et al.*, 2021; Perumal *et al.*, 2016; Sowmya *et al.*, 2021). Often, practitioners of modern (western) medicine describe traditional medicine using sceptical terms such as alternative, nonconventional, indigenous, and complementary, despite the fact that many of "modern" medicine's wound care techniques and practices are similar to traditional ones (Pei *et al.*, 2022; Jayaraj *et al.*, 2022; Palanisamy *et al.*, 2021). A majority of the world's population still values and practices traditional approaches that rely almost completely on natural resources, such as water, plants, animals, and minerals. Wound healing has been accelerated by natural extracts

(Perumal *et al.,* 2015; Sowmya *et al.,* 2015; Vidya *et al.,* 2016; Meganathan *et al.,* 2021; Sowmya *et al.,* 2015; Perumal *et al.,* 2015). In spite of this, there is limited scientific evidence that they are effective. The medical research community has always placed a great deal of importance on identifying the bioactive compounds in medicinally important herbal extracts and their mechanisms of action (Priyanga *et al.,* 2017; Kumar *et al.,* 2016; Malarvizhi *et al.,* 2015; Starlin *et al.,* 2012).

Mollugo nudicaulis Lam. (*M. nudicaulis*) is a plant belonging to the Molluginaceae family that is used for medicinal purposes in India. In Indian phytotherapy, it is traditionally used to treat wounds, coughs, colds, fevers, inflammation, cancer, and urinary and kidney infections (Palanisamy *et al.,* 2021). A phenolic extract of *M. nudicaulis* leaves exhibited anti-diabetic, anti-inflammatory properties in an animal model, and it also contains alkaloids, flavonoids, terpenoids, and other phenolic compounds. There are many plants used as Parpataka in different regions of India, so it is controversial to use the whole plant to prepare the Ayurvedic drug (Pratab *et al.,* 2021). Therefore, the current study aims to isolate the active compound from ethanolic extract of *M. nudicaulis* for *in vitro* and *in silico* wound healing applications.

MATERIAL AND METHODS

A. Plant collection

We collected the whole *M. nudicaulis* plant from Keeranur, Pudukkottai District, Tamil Nadu, India. This specimen has been authenticated by Dr. G.V.S. Murthy, Botanical Survey of India, Tamilnadu Agricultural University Campus, Coimbatore, Tamil Nadu (Reference: BSI/SRC/5/23/10-11/Tech 420). To ensure future analysis, the plant materials were further dried under shade, pulverized, and stored in an airtight jar at 4°C (Palanisamy *et al.,* 2021).

B. Extract preparation

Exhaustive extraction method was used to obtain extract from the plant material. Briefly, 600g of plant material was soaked in 3000 mL of ethanol-filled flask placed on a rotating shaker for 72 hours at average room temperature. At 40°C, a rotary evaporator (RE-2A evaporator) was used to concentrate the infusion. A storage temperature of 4°C was also maintained for future studies (Palanisamy *et al.,* 2022).

C. Compound isolation

We fractionated 20g of ethanolic extract of *M. nudicaulis* and eluted it with petroleum ether (90%), followed by petroleum ether: chloroform (8:2, 6:4, 4:4, 2:8 v/v). A 20 mL test tube was used to collect the column fractions. Each fraction was analyzed by thin layer chromatography (TLC) plates for a single spot for a total of 285 fractions (Palanisamy *et al.,* 2020).

D. Structural characterization

As part of the analysis of the presence of functional groups in an isolated compound, the Shimadzu FTIR-8400S Fourier Transform Infrared Spectrometer is used. Purged conditions are required for the operation of the spectrometer. Polyethylene pellets were used to disperse a solid sample of an isolated compound. The resolution of this instrument is typically 1.0/cm. It was possible to averaging signals, enhancing signals, adjusting baselines, and manipulating spectral information. A combination of spectroscopic techniques was used to unravel the structure of the isolated compound: mass spectrometry, ^{1}H and ^{13}C NMR, and two-dimensional experiments (correlation spectroscopy [COSY] and heteronuclear single quantum coherence [HSQC]). A Perkin-Elmer polarimeter (model 341) was used to determine optical rotation. As a reference, 500 MHz (^{1}H) and 125 MHz (^{13}C) NMR spectra of solutions in $CDCl_3$ were recorded on a Bruker DRX-500 NMR Spectrometer. Using mass spectrometry, the isolated compound's molecular mass was determined (Palanisamy *et al.,* 2019).

E. Selection and preparation of ligands

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

F. Selection and preparation of receptors

The Protein Data Bank (PDB) was used to obtain the crystal structures of wound healing target proteins. Chimera 1.16 was used to model the selected target proteins. Nonstandard heteroatoms were removed, polar hydrogens were added, and Gasteiger charges were added. An Amber force field (Amber FF14SB) was used to minimize energy for each protein using the steepest descent gradient method. Molecular docking was performed using the pdbqt format for converting the energy minimized protein (Anusooriya *et al.,* 2015).

G. Protein-ligand docking

The molecular docking of cmd-1 with selected wound healing target proteins was performed using Autodock Vina. The center of the grid box will display a ligand binding site if it is present. By setting a value of eight, the model is determined to be exhaustive. Discovery studio created a configuration file according to the XYZ axis dimensions determined by its visualizer. With Autodock Vina 1.1.2, a command-line configuration file was included for docking. A degree of flexibility is provided by the Monte Carlo algorithm when docking ligands. A Monte Carlo algorithm is used by Autodock Vina in comparison to other docking programs. Besides the results file, a single file containing binding modes (PDBQT format) was generated. BIOVIA Discovery Studio was used to analyze the binding interactions between the best docked ligands and receptors. Strong hydrogen bonds between heavy atoms ranged from 2.2 to 2.5, moderate hydrogen bonds between 2.5 to 3.2, and weak hydrogen bonds between 3.6 and 4.2 (Kannayiram *et al.,* 2022).

ADME properties prediction. QikProp (Schrodinger Suite 2022) was used to predict ADME properties. A ligand's pharmacokinetic and pharmacodynamic properties can be determined with QikProp by comparing them to the properties of drugs. It was

considered that the logarithm of the n-octanol/water partition coefficient as well as the molecular weight (MW) of the compound were important ADME properties (Table 1) (Palanisamy *et al.,* 2019).

Table 1: ADME properties of cmd-1 and nitrofurazone.

Compound name	Mol. Wt	H. Bond Donor	H. Bond Acceptor	Log P	Rotatable Bond
Cmd-1	428.55	3	7	6.8	19
Standard Drug (nitrofurazone)	198.1	2	5	0.2	2

H. In vitro cytotoxicity analysis

Cell line and culture. In order to carry out this study, NCCS Pune, India provided HUVEC and NHDF cell lines. A humidified atmosphere containing 5% CO_2 was used to maintain 37°C during the experiment. DMEM medium supplemented with 10% FBS and 1% antibiotics (100 U/mL penicillin and 100 U/mL streptomycin) was used to grow cells in T-25 flasks. Trypsinization and passage were performed once the cells reached confluence.

Cell viability analysis. A 10 mg/mL concentration of cmd-1 stock solutions was diluted in DMSO in culture media. 96-well plates were seeded with 5×10^3 cells and incubated at 37°C and 5% CO_2 for 24 hours to determine cell viability. A 24-hour incubation was conducted in DMEM medium supplemented with various concentrations of cmd-1 (0, 10, 20, 50, 100 and 200 µg/mL). After being incubated with cmd-1 for two hours, the cells were incubated in growth media containing 20% MTS solution. Microplate readers were used to measure the absorbance of formazan at 490 nm. Due to the high concentration of DMSO in the vehicle culture medium, cmd-1 was dissolved in 0.5% DMSO (Palanisamy *et al.,* 2021).

I. Statistical analysis

GraphPad Prism version 5 was used to conduct one-way analysis of variance and Duncan's multiple range test to determine whether there were significant differences between the control and treatment groups. Statistical significance was determined by Duncan's test at P=0.05 (Manimaran *et al.,* 2022).

RESULTS AND DISCUSSION

A. Compound isolation and structural characterization

Plant extracts contain natural compounds, but they may not be extracted using one solvent alone. Compounds elute from different solvents depending on their polarity. A significant role is played by these natural constituents of medicinal plants, which include alkaloids, tannins, flavonoids, steroid, terpenoid, carbohydrate, and phenolic compounds. It is possible to obtain accurate information regarding the qualitative and quantitative composition of herbal medicines by identifying natural compounds using chromatography and spectroscopy methods (Poornima *et al.,* 2017). In chemistry, compositions are separated from mixtures by column chromatography. Typically, it is used for preparative purposes on a scale ranging from micrograms to kilograms. As the main advantage, the stationary phase used in the process is relatively inexpensive and disposable. Due to recycling, cross-contamination and stationary phase degradation are prevented (Ragavendran *et al.,* 2012).

The ethanolic extract of *M. nudicaulis* was subjected to column chromatography by using different solvents such as petroleum ether and chloroform in the increasing order of polarity and the fractions were collected. A total of 285 fractions were collected, among which cmd-1 was identified from fraction number 224-238 with the R_f value 0.41 cm using TLC analysis. Fig. 1, indicates that only one compound may be present in this fraction. The single fraction yielded approximately 0.93 grams of pure compound that was used for further research. According to the UV-visible spectroscopy analysis, cmd-1 exhibits the most significant absorption bands at °max of 259 nm and at maximum absorbance was 0.378, which indicates the presence of single compound.

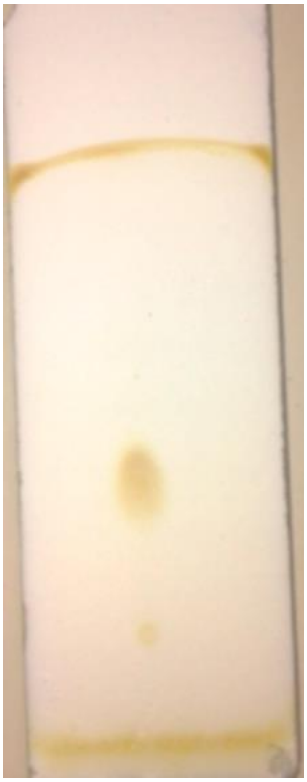

Fig. 1. Thin layer chromatography (TLC) analysis of cmd-1.

According to the FTIR spectrum (Fig. 2), the OH group exhibited characteristic absorption bands at 3392 cm^{-1}, a C=C bond at 1612 cm^{-1}, a C=O bond at 1714 cm^{-1}, and a C-H group at 2929, 1462, and 1376 cm^{-1}. The ^1H NMR spectrum (Fig. 3) of the compound displayed an up field signal at δ 0.85 for terminal methyl groups, a broad singlet at δ 1.28 and a multiplet at 1.59 for a long chain of methylene groups and a signal at δ 2.02 for a methylene group connected to the unsaturated group. Further a pair of multiplets at δ5.1& 5.6 appeared for unsaturated protons. The bunch of signals at δ 4.40, 4.1, 3.90, 3.68, 3.39, 3.21 suggests the presence of a sugar unit. The 13C NMR spectrum (Fig. 3) of the compound displayed signals at δ 14.10 for a terminal methyl group and signals at δ 22.68, 27.95, 27.97, 29.35, 29.65,

29.69, 30.21, 31.440, 32.81 are due to long chain methylene groups. The signals at δ 37.29 and 39.35 are due to α-methylene group carbons to the C=C. Further the signals at δ61.41, 65.48 and 72.92 suggests the presence of a sugar unit. The signals at δ 114.42, 124.46, 132.17 and 142.81 confirm the presence of double bonds in the compound. The signal at δ159.52 shows the presence of a carbonyl group. Thus, all the above spectral studies revealed that, the isolated compound was characterized and the assumed structure of the compound as 12-(10-carboxydecanoyloxy)-12-oxododecanoic acid (Fig. 4), its molecular weight 428.55 g/mol and molecular formula is $C_{23}H_{40}O_7$.

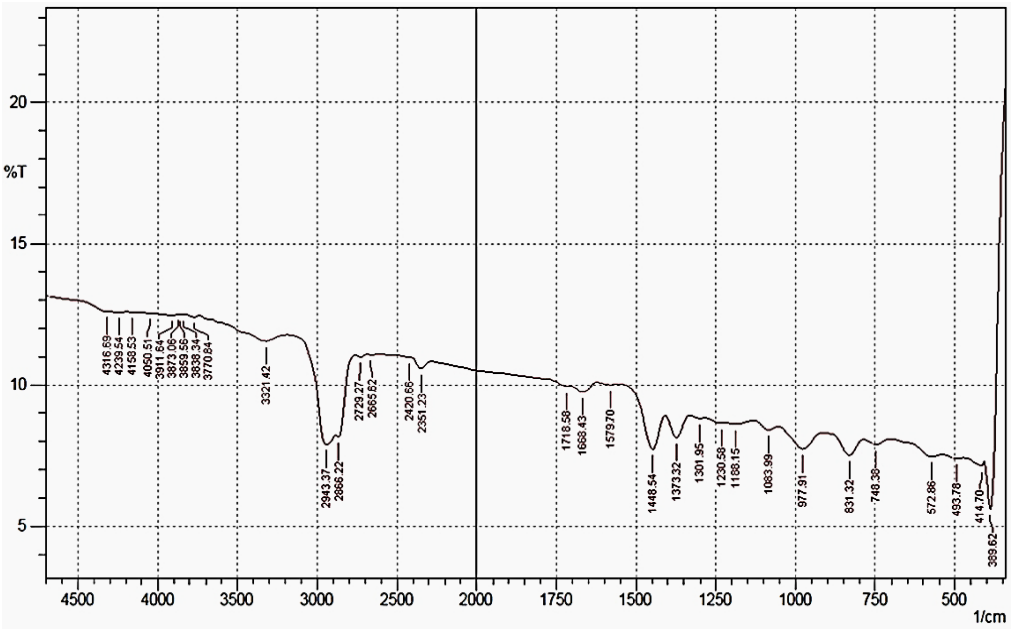

Fig. 2. Fourier Transform Infrared Spectrometer (FT-IR) analysis of cmd-1 which indicates presence of functional groups by the characteristic absorptions (1/cm).

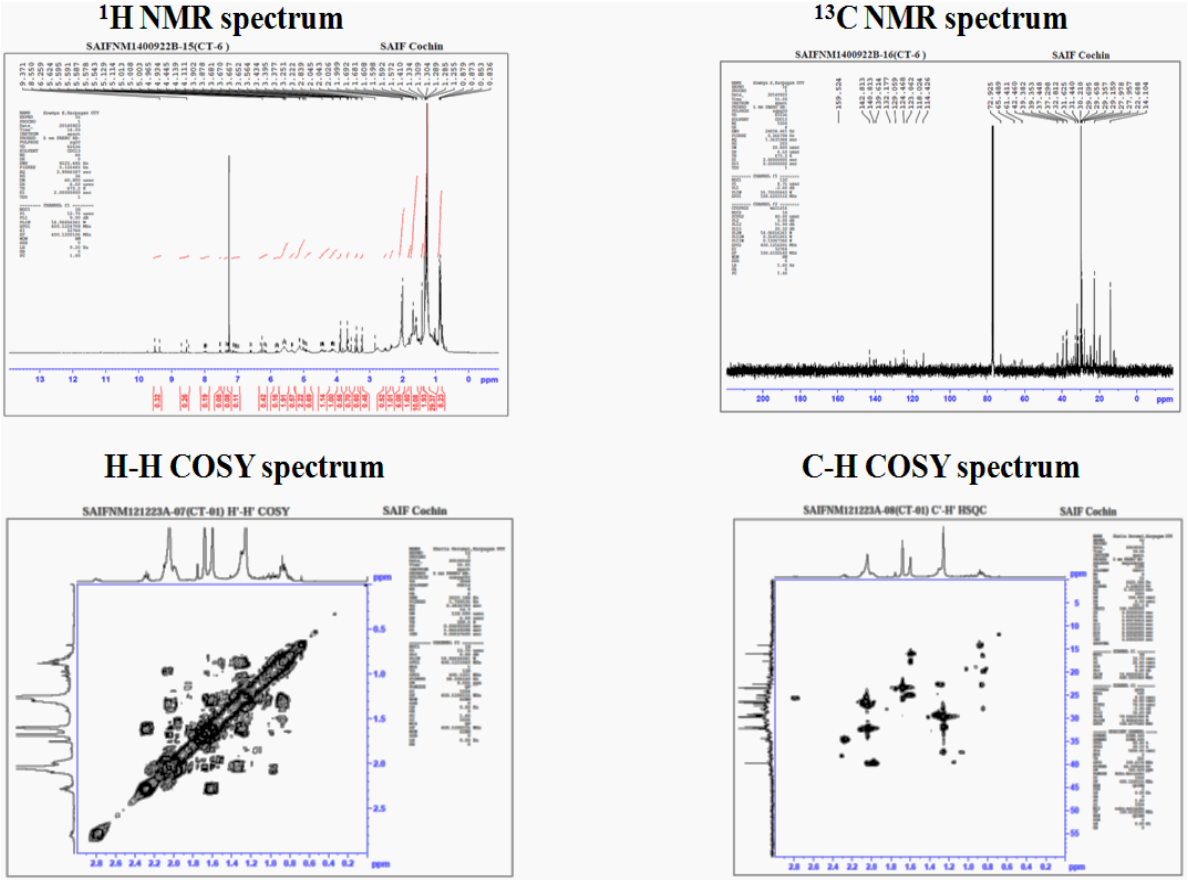

Fig. 3. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy analysis of cmd-1.

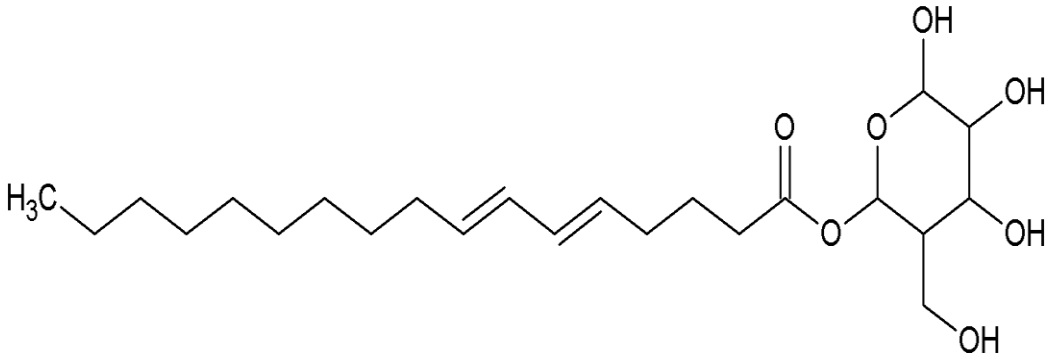

Fig. 4. Structure of isolated bioactive compound (cmd-1).

B. Computational analysis

This study used Autodock vina to predict cmd-1 binding affinity with target proteins (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) in wound healing process as well as standard drug (nitrofurazone). All target proteins bind to the isolated bioactive compound similarly, as shown in Fig. 5-10 and Table 1.

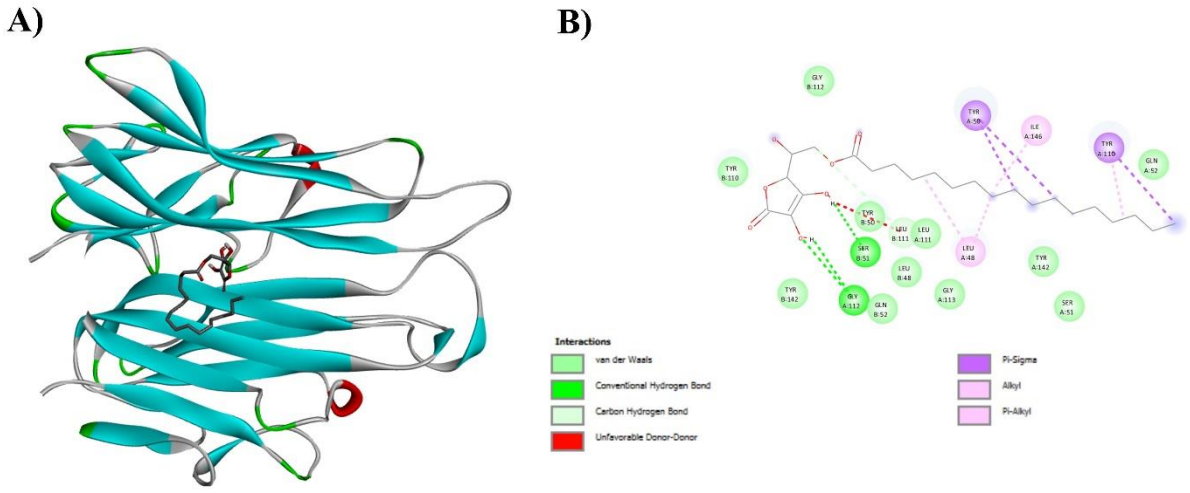

Fig. 5. Docking analysis of cmd-1 complexed with TNFα. A) 3D structure of docked complex and B) 2D structure of docked complex.

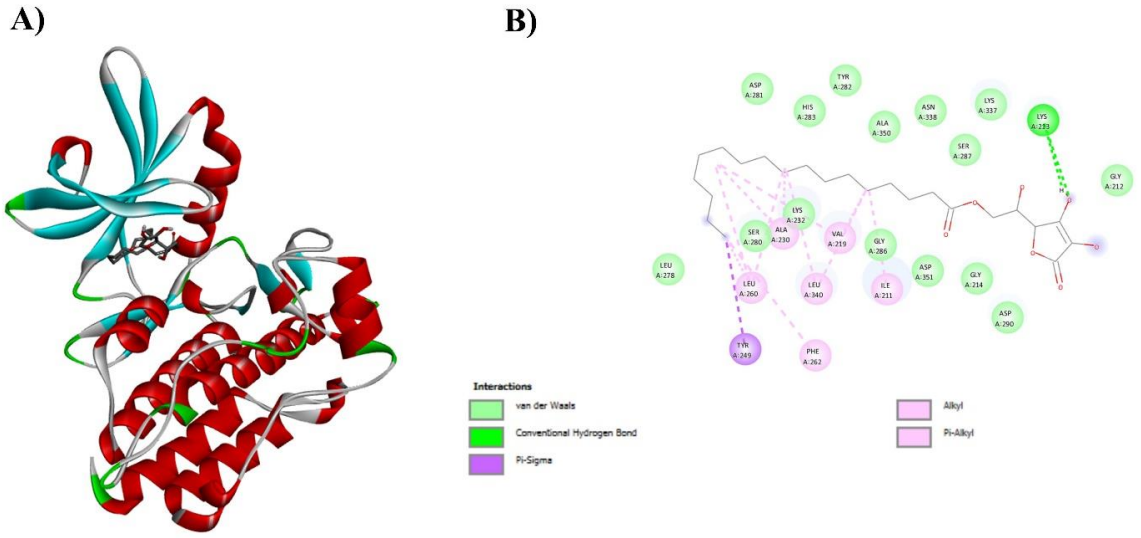

Fig. 6. Docking analysis of cmd-1 complexed with TGFBR1 kinase. A) 3D structure of docked complex and B) 2D structure of docked complex.

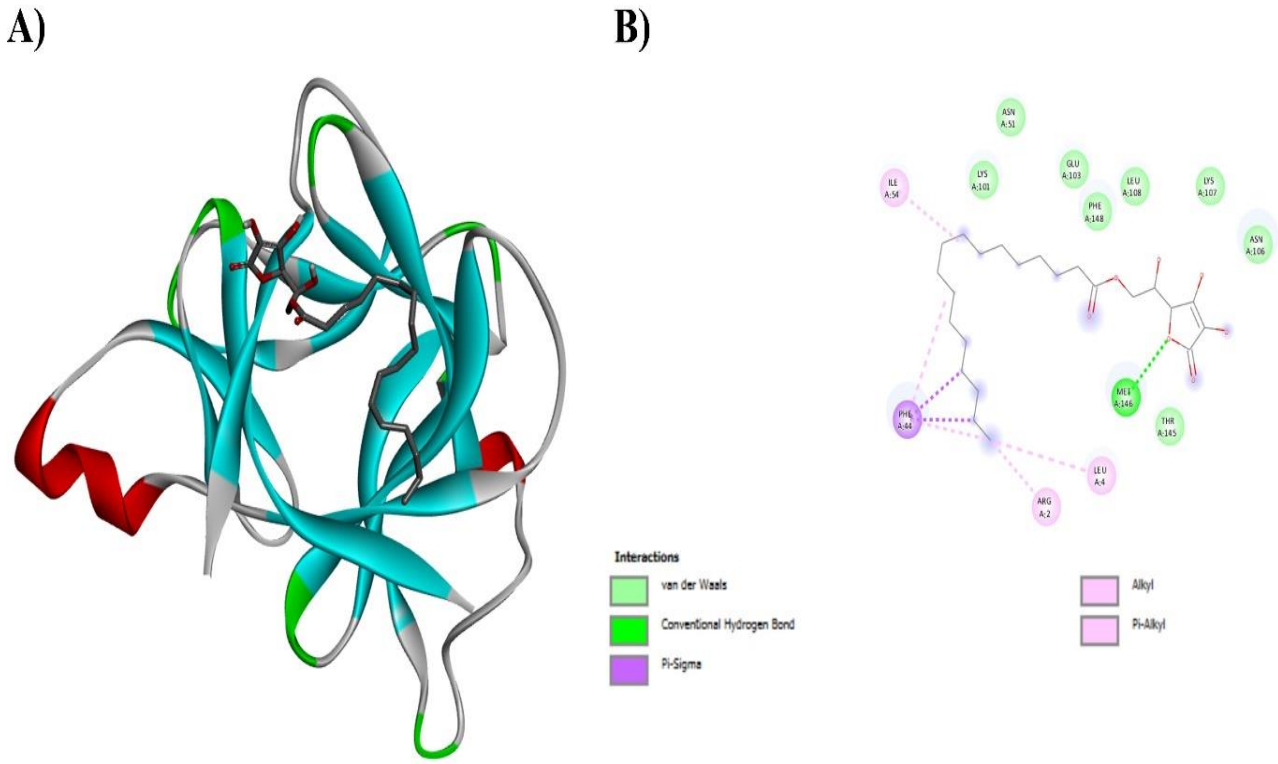

Fig. 7. Docking analysis of cmd-1 complexed with IL-1β. A) 3D structure of docked complex and B) 2D structure of docked complex.

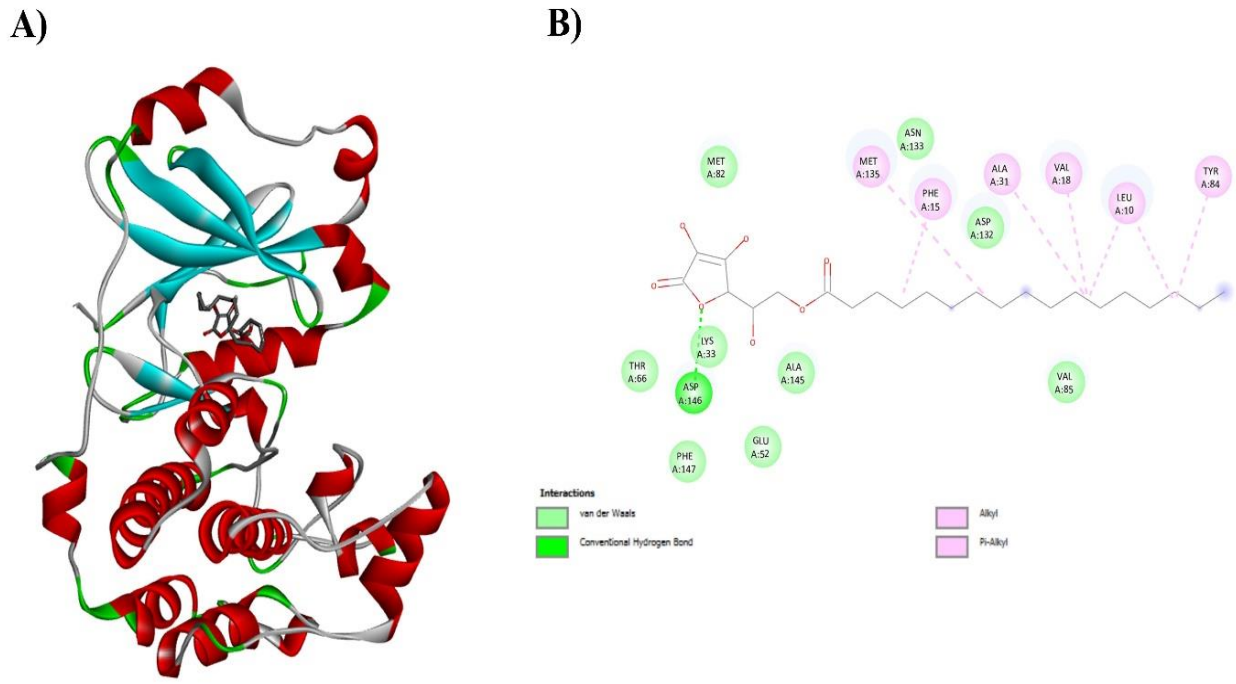

Fig. 8. Docking analysis of cmd-1 complexed with PKC-βII. A) 3D structure of docked complex and B) 2D structure of docked complex.

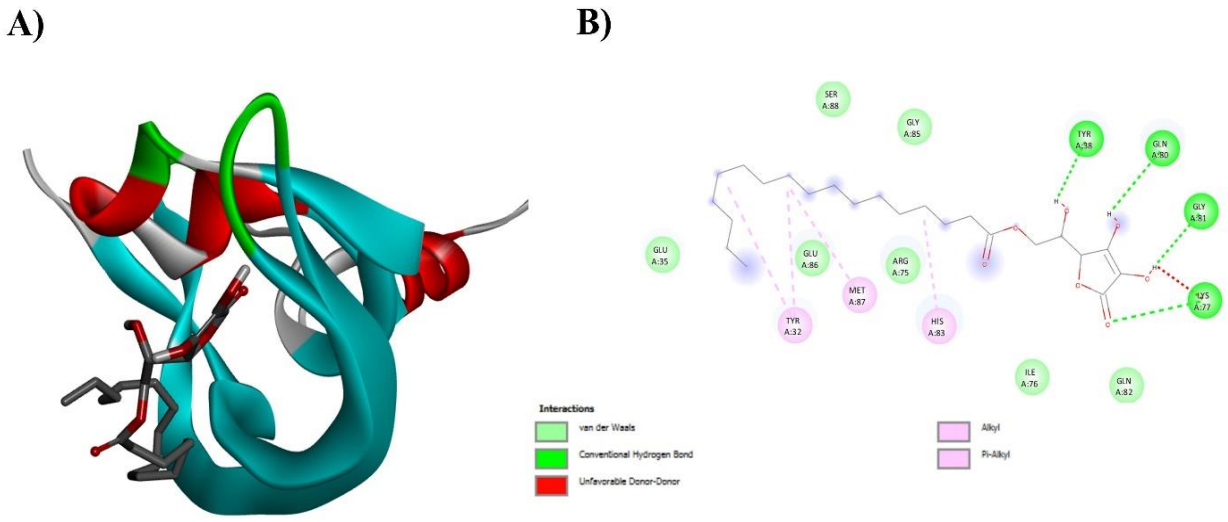

Fig. 9. Docking analysis of cmd-1 complexed with VEGF-A. A) 3D structure of docked complex and B) 2D structure of docked complex.

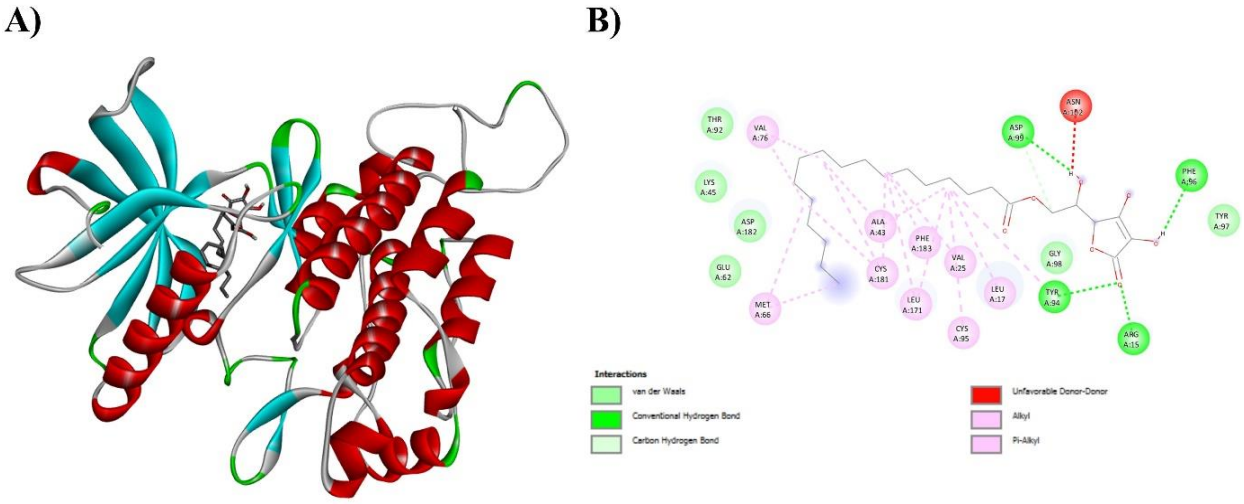

Fig. 10. Docking analysis of cmd-1 complexed with PDGFRA. A) 3D structure of docked complex and B) 2D structure of docked complex.

Table 2: Docking analysis of cmd-1 and standard drug of nitrofurazone complexed with wound healing target proteins.

Sr. No.	Target Proteins (PDB ID)	Cmd-1 (kcal/mol)	Standard Drug (kcal/mol)
1.	TNFα (2AZ5),	-6.3	-5.8
2.	TGFBR1 kinase (6B8Y),	-6.6	-6.2
3.	IL-1β (6Y8M),	-4.6	-4.0
4.	PKC-βII (PDB: 2I0E),	-5.8	-5.9
5.	VEGF-A (3QTK)	-4.0	-4.6
6.	PDGFRA (6JOL).	-6.9	-6.9

A wound that is inflamed is caused by a high level of tumor necrosis factor alpha (TNFα). Evidence suggests that inhibition of TNFα is a critical for treatment of wounds. It supports reepithelialization, inflammation, angiogenesis, and new tissue growth in wound healing. Phytocompounds of cmd-1 have been studied for their potential therapeutic effects on wound healing-related molecular targets, we have performed docking studies with TNFα, TGFBR1 kinase, IL-1β, PKC-βII, VEGF and PDGF. Based on docking studies, we predicted that

an isolated bioactive compound of 12-(10-carboxydecanoyloxy)-12-oxododecanoic acid would have strong binding affinity for selected wound healing targets.

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

It's expected that ideal wound dressing should greatly be compatible. MTS assay was used to verify the cell viability and cytocompatibility ofcmd-1. The cytotoxicity of the isolated bioactive compound of 12-(10-carboxydecanoyloxy)-12-oxododecanoic acid (cmd-1) at different concentrations were tested using two different fibroblast cell lines (NHDF and HUVEC). As shown in Fig. 11, cmd-1 at the highest concentration, 200 µg/mL, had no cytotoxic effect on fibroblast cell lines when plotted against its treatment concentrations.

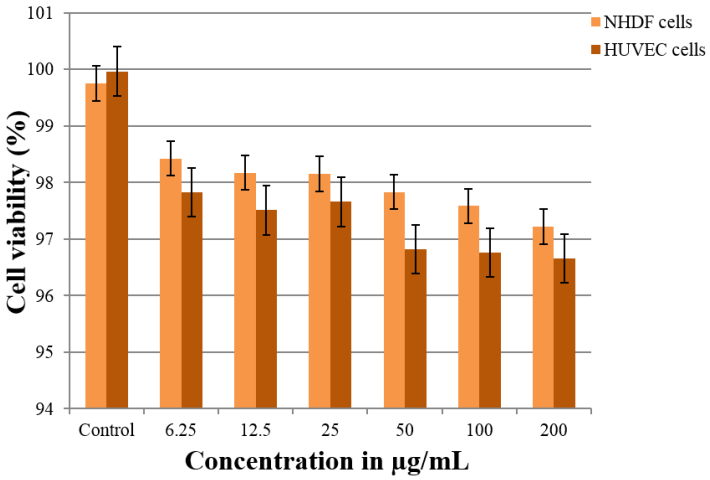

Fig. 11. Effect of cmd-1 on cell viability of NHDF and HUVEC cells.

CONCLUSIONS

Using chromatographic and spectroscopic methods, ethanolic extract of *M. nudicaulis* was used to isolate and identify bioactive compound of 12-(10-carboxydecanoyloxy)-12-oxododecanoic acid (cmd-1). In vitro cytotoxicity tests of cmd-1 on NHDF and HUVEC fibroblast cell lines did not show cytotoxicity at highest concentrations of 200 µg/mL. In a computational docking study associated with cmd-1, it was noted that it had good interaction with the wound healing targets of TNFα, TGFBR1 kinase, IL-1β, PKC-βII, VEGF and PDGF with docking scores ranging from -4.0 to -6.9 Kcal/mol. The ADME properties of those compounds were acceptable. In vitro and in silico results indicate that 12-(10-carboxydecanoyloxy)-12-oxododecanoic acid isolated from ethanolic extract of *M. nudicaulis* may have wound healing properties. Further research on *in vitro* and *in vivo* experimental animal models is required before the current funding can be confirmed.

FUTURE SCOPE

The bioactive compound of 12-(10-carboxydecanoyloxy)-12-oxododecanoic acid isolated from ethanolic extract of *M. nudicaulis* could act as a novel therapeutic agent for wound healing applications. 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.

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

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