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Original Article

Isorhamnetin as a Potential Therapeutic Agent for Diabetic Wound Healing: *In silico* Evaluation of Collagen Synthesis and Fibroblast Proliferation with *in vitro* Antioxidant Validation

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ABSTRACT

Background: Chronic non-healing wounds, which occur in most cases of diabetic wound healing due to persistent oxidative stress, disordered collagen deposition, impaired fibroblast proliferation, and imbalance in growth factor signalling, represent a major medical problem. Currently, there are a variety of treatment options but all are expensive, require long treatment courses, and are difficult to treat. Therefore, natural flavonoids exhibiting antioxidant and wound-healing properties could be potent candidates for diabetic wound repair. Isorhamnetin, a well-established biologically active component of *Petroselinum crispum* that is a typical member of flavonoid glycosides, exhibits varied pharmacological properties; nevertheless, its underlying molecular mechanisms in the process of diabetic wound repair have not been thoroughly evaluated. **Objectives:** In this study, the therapeutic potential of isorhamnetin in diabetic wound healing was explored based on the comprehensive *in vitro* antioxidant activity assays and *in silico* molecular docking and protein-protein interaction analyses, in an effort to elucidate the underlying molecular targets of this potent bioactive flavonoid. **Materials and Methods:** Antioxidant properties of methanol extract of *P. crispum* were evaluated by the DPPH radical scavenging capacity and the SOD-like activity. Antioxidant evaluation of the extract was performed using the DPPH radical scavenging and SOD-like activities. Ascorbic acid was used as a positive control and a reference standard. Molecular docking was carried out with AutoDock Vina software to simulate binding of isorhamnetin with important wound-healing targets including PDGF-BB, PDGFR- β, VEGF-A, TGF- β1, MMP-9 and Nrf2. Binding affinities of isorhamnetin to targets were compared to metformin. Additionally, protein-protein docking analysis between becaplermin and PDGFR- β was evaluated to explore the possible roles of PDGF in fibroblast activation and neovascularization. **Results:** The methanol extract of *P. crispum* showed significant concentration-dependent DPPH free radical scavenging (IC_{50}=65.08 µg/mL) and SOD-like activity (IC_{50}=70.98 µg/mL), which was comparable to ascorbic acid. Molecular docking revealed high affinities of isorhamnetin for PDGFR- β (10.0 kcal/mol), Nrf2 (9.6 kcal/mol) and MMP-9 (8.8 kcal/mol), along with a well predicted interaction for TGF- β1 (8.4 kcal/mol), VEGF-A (7.4 kcal/mol), and PDGF-BB (6.6 kcal/mol). The binding affinities of metformin to the targets tested were comparatively lower than isorhamnetin (ranging from 4.5 to 6.3 kcal/mol). Moreover, protein-protein docking suggested that there is a stable interaction between becaplermin and PDGFR- β (13.4 kcal/mol), confirming the essential role of PDGF signalling in activating fibroblasts and facilitating angiogenesis. **Conclusion:** The present research indicates that isorhamnetin can play a beneficial role in diabetic wound healing by the dual mechanism of enhancing antioxidant activity and modulating the targets of fibroblast proliferation, angiogenesis, extracellular matrix remodeling and regulation of reactive oxygen species production. These results may highlight *P. crispum* as a potentially valuable source for isorhamnetin, and lay a good scientific basis for subsequent *in vivo* study to evaluate isorhamnetin as a natural drug for diabetic wound therapy.

Keywords: Antioxidant activity, Diabetic wound healing, Isorhamnetin, Molecular docking, *Petroselinum crispum*.

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INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder with persistent hyperglycemia and associated complications in the body and is associated with numerous organ systems. One of the most challenging complications of diabetes is wound healing, leading

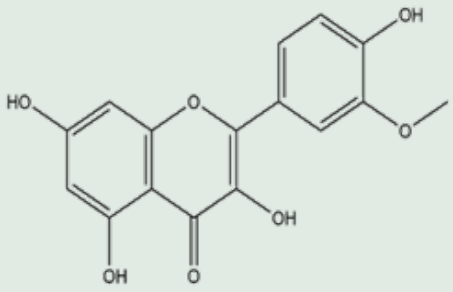
to chronic wounds like diabetic foot ulcers. These wounds are associated with prolonged inflammation, excessive oxidative stress, reduced angiogenesis, impaired fibroblast proliferation, and abnormal extracellular matrix remodeling, and so the delayed wound healing significantly increases the risk of infection, amputation, and morbidity in diabetic patients. Despite the availability of several therapeutic options, managing diabetic wounds is still a major clinical problem.

Oxidative stress plays a critical role in diabetic wound healing. Increased levels of Reactive Oxygen Species (ROS) are associated with damage to cell membranes (proteins, lipids, and DNA) and the normal repair process. Excessive ROS production results in a clash between the pro-oxidant and antioxidant processes, which results in a slower proliferation of fibroblasts, reduced collagen synthesis, and impaired angiogenesis. Therefore, compounds with antioxidant activity can help restore redox balance and assist wound healing. Besides oxidative stress, other growth factors and signaling pathways are critical in wound healing. Platelet-Derived Growth Factor (PDGF) and its receptor PDGFR-β are key factors in promoting fibroblast proliferation, migration, and collagen formation in the proliferative stage of wound healing (Yoon *et al.*, 2021).

Similarly, Vascular Endothelial Growth Factor (VEGF) is critical in angiogenesis to maintain sufficient blood supply and nutrients for regeneration. Transforming Growth Factor-β (TGF-β) controls extracellular matrix formation and fibroblast development, and matrix metalloproteinases such as MMP-9 control extracellular matrix remodeling. In addition, Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2) is a key transcription factor that regulates cellular antioxidant defense mechanisms since it controls antioxidant enzymes. Natural products have received a lot of attention as treatment agents for chronic wounds due to their rich pharmacological properties and relatively low toxicity (Kaussikaa *et al.*, 2024).

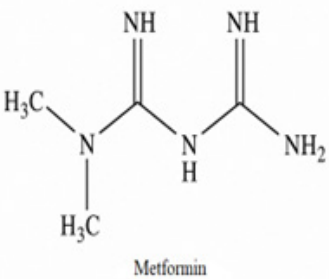
Medicinal plants are a great source of phytochemicals with bioactive properties of flavonoids, phenolic acids, and terpenoids, and many of them have antioxidant, anti-inflammatory, and tissue-regenerative properties (Chanu *et al.*, 2023). *Petroselinum crispum* (parsley) is another commonly used culinary and medicinal plant that has a variety of phytoconstituents with major biological activity. One of the most well-tolerated products for the treatment of chronic wounds is isorhamnetin, a methylated flavonol, which has shown to have antioxidant, anti-inflammatory, and cytoprotective properties in the blood and body. Recently, isorhamnetin has been suggested to be effective in cell repair and may play a role in tissue repair through reduction of oxidative stress and regulation of multiple signaling pathways involved in cell proliferation and angiogenesis (Gong *et al.*, 2020). The molecular mechanisms of how isorhamnetin is involved in diabetic wound healing have not been fully understood, however. Computational approaches such as molecular docking are useful tools to predict the interaction of bioactive compounds with target proteins and the disease pathway. Such *in silico* approaches allow the identification of potential therapeutic targets and insights for drug and protein interactions. Therefore, in this work, we aimed to study the therapeutic role of isorhamnetin for diabetic wound healing in both *in vitro* and *in silico* studies. *Petroselinum crispum* extract was investigated for its antioxidant activity with DPPH and superoxide radical scavenging assays to confirm the ability of the extract to remove reactive oxygen species (Rashidi *et al.*, 2023; Liu *et al.*, 2021).

In addition, molecular docking studies were carried out to investigate the binding of isorhamnetin to various proteins involved in wound healing processes such as PDGF-BB, PDGFR-β, VEGF-A, TGF-β1, MMP-9, and Nrf2. Furthermore, docking of becaplermin with metformin and protein-protein docking of PDGFR-β was also performed to better understand the therapeutic relevance of PDGF signaling in diabetic wound healing. By combining antioxidant analysis with molecular docking analysis, we hope to provide mechanistic insights on the potential of isorhamnetin as a multi-target therapeutic candidate which can be used to modulate oxidative stress, fibroblast



Isorhamnetin

3,5,7-trihydroxy-2-(4-hydroxy-3-methoxyphenyl)-4*H*-chromen-4-one
Chemical Formula: $C_{16}H_{12}O_7$
Molecular Weight: 316.27



Metformin

1,1-Dimethylbiguanide
Chemical Formula: $C_4H_{11}N_5$
Molecular Weight: 129.16

proliferation, angiogenesis, and extracellular matrix remodeling in diabetic wound healing (Pinzi and Rastelli, 2019).

MATERIALS AND METHODS

Chemicals and Reagents

All the chemicals and reagents used in the present study were of analytical grade and were bought from the commercial suppliers. The 2,2-Diphenyl-1-picrylhydrazyl (DPPH, CAS No. 1898-66-4), nitro blue tetrazolium (NBT, CAS No. 298-83-9), riboflavin (CAS No. 83-88-5), L-methionine (CAS No. 63-68-3), and Ethylenediaminetetraacetic Acid (EDTA, CAS No. 60-00-4) were bought from Sigma-Aldrich (St. Louis, MO, USA). Potassium phosphate buffer was made by dissolving KH_2PO_4 (CAS No. 7778-77-0) in water and then adding K_2HPO_4 (CAS No. 7758-11-4). The antioxidant standard used was ascorbic acid (CAS No. 50-81-7). All solvents in this study were analytical grade and obtained from Merck Life Science Pvt. Ltd., (Mumbai, India). All reagents were used as received and fresh solutions were used for the experimental analysis.

Plant Material and Preparation of Extract

Fresh plant material of *Petroselinum crispum* was collected and authenticated as per standard botanical identification processes. The plant material was thoroughly washed with distilled water to remove impurities and shade-dried at room temperature. The dried plant material was then powdered with a mechanical grinder. The powdered material was then purified and extracted with ethanol as solvent. The extract was filtered and concentrated with a rotary evaporator under reduced pressure to give a semi-solid crude extract. The dried extract was stored in airtight containers at 4°C until further antioxidant assays were carried out (Al-Gamli *et al.*, 2026).

In vitro Antioxidant Assays

DPPH Radical Scavenging Assay

In addition, the DPPH radical scavenging activity of *Petroselinum crispum* extract was measured by the standard spectrophotometric method. A fresh DPPH solution (0.1 mM) was prepared in methanol as the free radical reagent. Different concentrations of plant extract were prepared in methanol. An aliquot of each concentration of the extract was mixed with DPPH solution and incubated in the dark at room temperature for about 30 min for the reaction to take place. The reduction of the DPPH radical was observed by measuring the decrease in absorbance at 517 nm on the UV-visible spectrophotometer. Ascorbic acid was used as a standard antioxidant for comparison. The percentage inhibition of DPPH radicals was calculated using formula (Upadhyay *et al.*, 2010).

$$Scavenging\ activity\ (\%) = \frac{Absorbance_{control} - Absorbance_{sample}}{Absorbance_{control}} \times 100$$

The concentration required to inhibit 50% of the DPPH radicals (IC_{50}) was determined from the inhibition curve.

Superoxide Radical Scavenging (SOD-like) Assay

The superoxide radical scavenging activity of the extract was studied using the riboflavin-light-NBT system. The reaction mixture was composed of phosphate buffer (pH 7.8), methionine, riboflavin, EDTA, and Nitro Blue Tetrazolium (NBT). Different concentrations of the extract were added to the reaction mixture. The reaction was started by exposing the mixture to fluorescent light for a fixed amount of time, leading to the formation of superoxide radicals. These radicals reduce NBT and give rise to the blue-colored formazan product, which can be measured spectrophotometrically. The absorbance was measured at 560 nm using a UV-visible spectrophotometer. Ascorbic acid was used as the standard reference compound. The percentage inhibition of superoxide radicals was calculated according to equation (Apak *et al.*, 2016).

$$Scavenging\ activity\ (\%) = \frac{Absorbance_{control} - Absorbance_{sample}}{Absorbance_{control}} \times 100$$

The IC_{50} values were calculated from the inhibition curve to determine the antioxidant potency of the extract.

Molecular Docking Study

Ligand Preparation

The chemical structure of isorhamnetin, a major flavonoid component of *Petroselinum crispum*, was downloaded from the PubChem database. The three-dimensional structure was downloaded in suitable format and optimized using molecular modeling software to obtain the lowest energy conformation before docking analysis. The standard drug metformin was also retrieved from the PubChem database and prepared using the same procedure for comparative docking analysis (Taherkhani *et al.*, 2021).

Protein Preparation

The three-dimensional crystal structures of the target proteins involved in diabetic wound healing were retrieved from the Protein Data Bank (PDB). The selected wound-healing protein targets are presented in Table 1. The protein structures were prepared by removing water molecules and co-crystallized ligands. Hydrogen atoms were added, and the structures were energy minimized prior to docking analysis (Rana *et al.*, 2025).

Molecular Docking Procedure

The molecular docking simulation was performed with AutoDock Vina to check the interactions between isorhamnetin and the protein targets. Grid boxes are drawn around the active binding sites of the proteins to induce flexible docking. Docking produced several possible binding positions and the best binding approach was selected based on the lowest binding energy score (kcal/mol).

The interactions between the ligand and amino acid residues in the binding pocket were measured with molecular visualization tools (Zheng *et al.*, 2026).

Docking Validation

In order to validate the docking protocol, we re-docked the co-crystallized ligand of each protein target into the binding pocket by using the same docking parameters. The docking protocol was considered reliable when the RMSD between the experimental and predicted ligand conformations was less than 2.0 Å. The docking grid dimensions, exhaustiveness value (8), and energy range (3 kcal/mol) were kept the same in all docking simulations (Liu *et al.*, 2024).

Comparative Docking with Standard Drug

To check the relative binding affinity of isorhamnetin, docking analysis is also performed with metformin, a commonly used oral antidiabetic drug. The docking scores of metformin are compared with the docking scores of isorhamnetin for the selected protein targets (Pu *et al.*, 2023).

Protein-Protein Docking Analysis

Protein docking analysis was performed for becaplermin (recombinant human PDGF-BB) and its primary receptor PDGFR-β, which is important for fibroblast proliferation and wound healing. The docking analysis was also performed to examine potential interactions with other growth factors, such as VEGF-A and TGF-β1, for wound repair. The docking results were analyzed on the basis of binding energy, interaction interface, and stability of the protein complexes (Alqudah *et al.*, 2024).

Statistical Analysis

The antioxidant experiments were performed in triplicate (n=3) and all experimental data were presented as mean±Standard Deviation (SD). Statistical analyses were performed using GraphPad Prism version 10.0 (GraphPad Software Inc., San Diego, CA, USA). The difference between the methanolic extract of *Petroselinum crispum* and the reference standard (ascorbic acid) at corresponding concentrations was analyzed using one-way Analysis of Variance (ANOVA) followed by Tukey's multiple comparison post hoc test. The IC_{50} values for DPPH and superoxide radical scavenging assays were calculated using nonlinear regression analysis based on concentration-response curves. A value of $p<0.05$ was considered statistically significant. For molecular docking, binding affinity values derived using AutoDock Vina version 1.2.5 were ranked by binding free energy (kcal/mol). The docking poses with the lowest binding energy and good hydrogen bonding and hydrophobic interactions in the active site were selected for further analysis using Discovery Studio Visualizer 2024 and PyMOL version 3.0 (Chi *et al.*, 2022; Sindhuja *et al.*, 2021).

Ethics Statement

The present investigation involved only plant extract-based *in vitro* antioxidant assays and computational molecular docking analyses. No experiments involving human participants or laboratory animals were performed; therefore, approval from an Institutional Ethics Committee or Institutional Animal Ethics Committee was not required.

RESULTS

Antioxidant Activity of *Petroselinum crispum* Extract

DPPH Radical Scavenging Assay

The antioxidant activity of *Petroselinum crispum* extract was tested through the DPPH radical scavenging assay and compared to ascorbic acid as the standard. The extract showed free radical scavenging activity in all the samples. The IC_{50} value of the extract was 65.08 µg/mL while ascorbic acid was 58.64 µg/mL and the antioxidant power of the standard compound was slightly higher. At 50 µg/mL the extract was inhibited by 1.95% with an absorbance of 0.7384 and the ascorbic acid by 7.95% with an absorbance of 0.7171. Also, the extract showed less radical scavenging activity at the tested concentration than the standard. The DPPH radical scavenging activity is summarized in Table 2.

The concentration-dependent DPPH radical scavenging activity of *Petroselinum crispum* methanolic extract compared with the standard antioxidant (ascorbic acid) is illustrated in Figure 1.

Superoxide Radical Scavenging (SOD-like) Activity

The superoxide radical scavenging activity of *Petroselinum crispum* extract was evaluated using a riboflavin-light-NBT system. The extract exhibited dose-dependent inhibition of superoxide radicals when compared with the reference antioxidant, ascorbic acid. The IC_{50} value of the extract was found to be 70.98 µg/mL, whereas the IC_{50} value of ascorbic acid was 65.94 µg/mL. At a concentration of 50 µg/mL, the extract produced 2.96% inhibition with an absorbance value of 0.6627, while ascorbic acid showed 7.19% inhibition with an absorbance of 0.6492. These results indicate that *P. crispum* extract possesses moderate superoxide radical scavenging activity compared with the standard antioxidant. Superoxide radical scavenging activity is shown in Table 3. The concentration-dependent superoxide

Table 1: Selected protein targets and their Protein Data Bank (PDB) identifiers used for molecular docking analysis.

Protein Target	PDB ID
PDGF-BB	1PDG
PDGFR-β	5GRN
TGF-β1	3KFD
VEGF-A	1VPF
MMP-9	1GKC
Nrf2	4ZY3

radical scavenging activity of *Petroselinum crispum* extract compared with the reference standard is presented in Figure 2.

Molecular Docking Analysis

Our docking strategy is to compare the interaction of isorhamnetin in *Petroselinum crispum* with the main proteins involved in diabetic wound healing: PDGF-BB (1PDG), PDGFR-β (5GRN), TGF-β1 (3KFD), VEGF-A (1VPF), MMP-9 (1GKC), and Nrf2 (4ZY3). We used Metformin as reference drug. The docking showed isorhamnetin to be good at binding to all targets. The strongest binding affinity for PDGFR-β was with TGF-β1 (-10.0 kcal/mol), Nrf2 (-9.6 kcal/mol) and MMP-9 (-8.8 kcal/mol). There were small interactions with TGF-β1 (-8.4 kcal/mol), VEGF-A (-7.4 kcal/mol) and PDGF-BB (-6.6 kcal/mol). In particular, the ligand interactions were hydrogen bonding, hydrophobic interactions, π-π stacking, and metal coordination in the active binding pockets of the protein. These results indicate the potential multitarget role of isorhamnetin in diabetic wound healing by controlling angiogenesis, extracellular matrix remodeling, oxidative stress and tissue regeneration. Docking scores are presented in Table 4.

Representative molecular docking interactions of isorhamnetin and metformin with PDGF-BB (PDB ID: 1PDG) are illustrated in Figure 3, highlighting the binding conformations and key amino acid interactions within the active binding pocket. The comparative docking poses and interaction profiles of isorhamnetin and metformin with PDGFR-β (PDB ID: 5GRN), the principal regulator of fibroblast proliferation and angiogenesis, are presented in Figure 4. The molecular interactions of isorhamnetin and metformin with TGF-β1 (PDB ID: 3KFD), an important mediator of extracellular matrix synthesis and collagen deposition, are shown in Figure 5. Comparative molecular docking analysis of isorhamnetin and metformin with VEGF-A (PDB ID: 1VPF), a key regulator of angiogenesis during wound

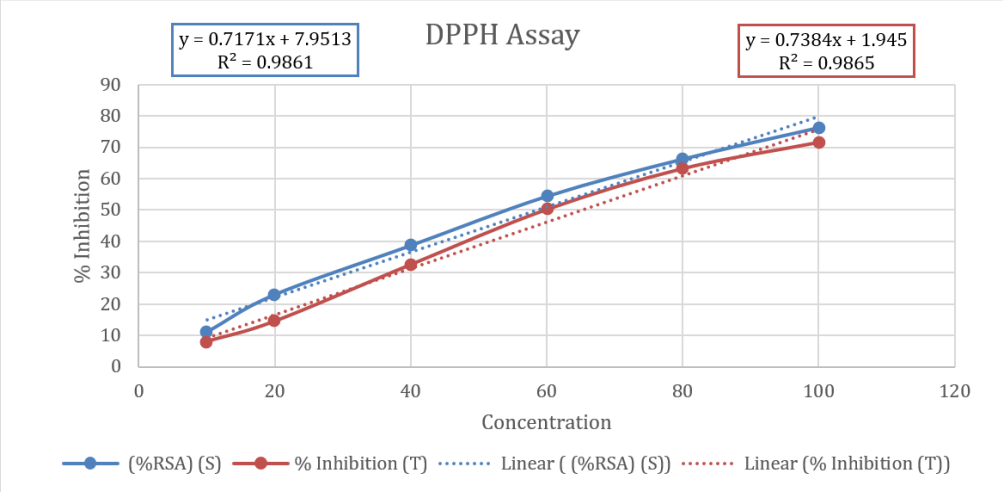
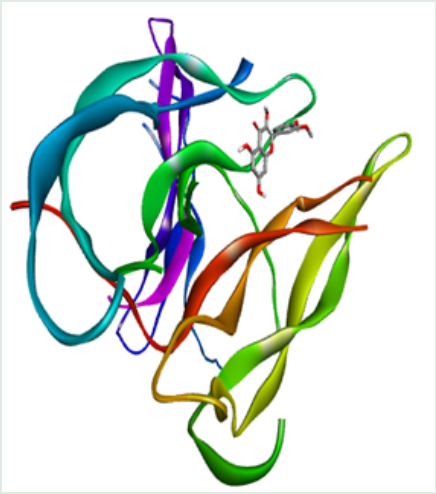
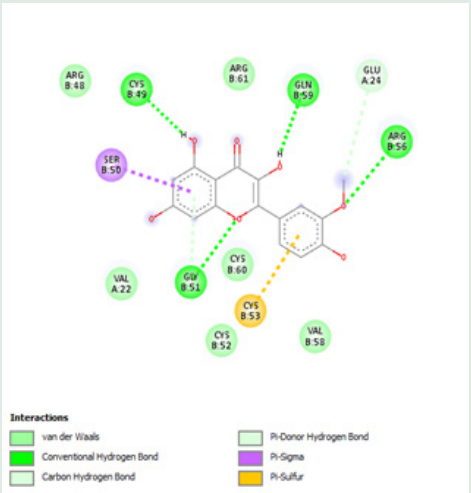


Figure 1: Concentration-dependent antioxidant activity of the extract determined by the DPPH Radical Scavenging Assay compared with the standard Ascorbic Acid.

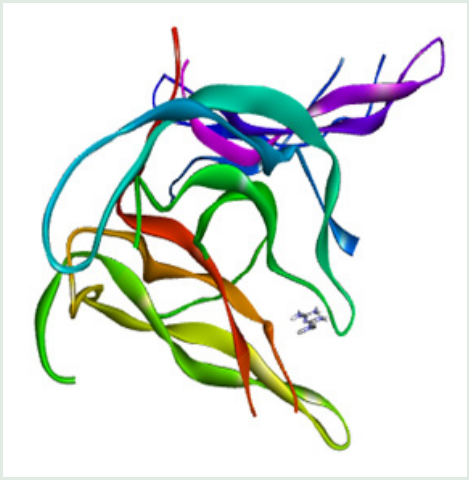
(A) Isorhamnetin - 1PDG (3D Binding Pose)



(B) Isorhamnetin - 1PDG (2D Interaction Map)



(C) Metformin - 1PDG (3D Binding Pose)



(D) Metformin - 1PDG (2D Interaction Map)

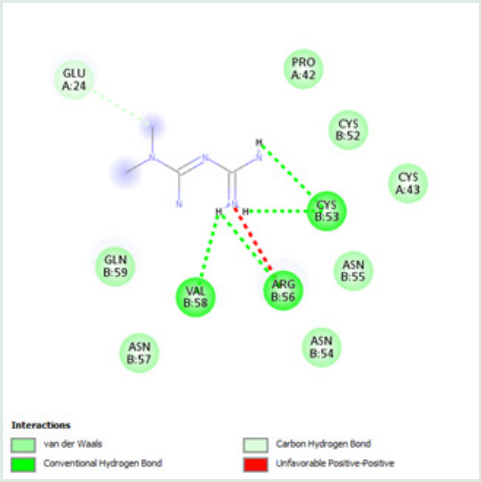


Figure 3: Representative docking poses and interaction profiles of isorhamnetin and metformin with PDGF-BB (PDB ID: 1PDG). (A) 3D binding pose of isorhamnetin, (B) 2D interaction map of isorhamnetin, (C) 3D binding pose of metformin, and (D) 2D interaction map of metformin, showing binding energies of -6.6 kcal/mol and -4.5 kcal/mol.

Table 2: DPPH radical scavenging activity of *Petroselinum crispum* methanolic extract and ascorbic acid at different concentrations.

Sl. No.	Concentration (µg/mL)	Control Absorbance	%RSA (Standard)	%RSA (Test)
1.	10	0.80	11.25	8.13
2.	20	0.80	23.13	14.62
3.	40	0.80	38.75	32.66
4.	60	0.80	54.38	50.23
5.	80	0.80	66.25	63.28
6.	100	0.80	76.25	71.65
IC_{50} Values				
	Sample		IC_{50} (µg/mL)	
	Standard (Ascorbic acid)		58.64	
	Standard (Ascorbic acid)		58.64	

Abbreviations: DPPH, 2,2-diphenyl-1-picrylhydrazyl; RSA, radical scavenging activity; IC_{50}, concentration required to inhibit 50% of free radicals

healing, is presented in Figure 6. The binding conformations and interaction maps of isorhamnetin and metformin with MMP-9 (PDB ID: 1GKC), an enzyme involved in extracellular matrix remodeling, are illustrated in Figure 7.

The molecular docking interactions of isorhamnetin and metformin with Nrf2 (PDB ID: 4ZY3), an essential regulator of cellular antioxidant defense mechanisms, are shown in Figure 8.

Comparative Docking with Standard Drug

In addition, we compared the docking properties of isorhamnetin and metformin as the known antidiabetic candidate. Isorhamnetin showed stronger binding affinity to all the wound healing targets than metformin. Among all the proteins, isorhamnetin exhibited the highest affinity to PDGFR-β (-10.0 kcal/mol) while metformin was less attractive (-5.0 kcal/mol). The higher affinity of isorhamnetin suggests that it is involved in fibroblast proliferation, angiogenesis, extracellular matrix remodeling, and oxidative stress during wound healing. Comparative docking results are summarized in Table 5.

Protein-Protein Docking Analysis of Becaplermin

We have conducted protein-protein docking analysis to compare the interaction between becaplermin and PDGFR-β as a topical drug for diabetic ulcers with its main receptor PDGFR-β. The docking results indicate that becaplermin binds PDGFR-β strongly and at a binding energy of -13.4 kcal/mol, indicating reliable binding of becaplermin to the receptor. Further interaction analysis demonstrated additional binding of becaplermin with VEGF-A (-10.1 kcal/mol) and TGF-β1

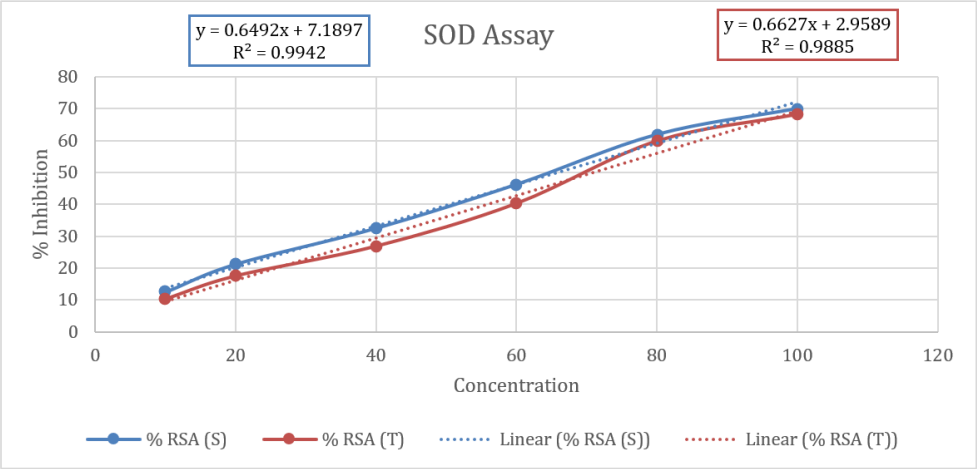


Figure 2: Superoxide radical scavenging activity of the extract evaluated using the Superoxide Dismutase Assay with Ascorbic Acid as the reference standard.

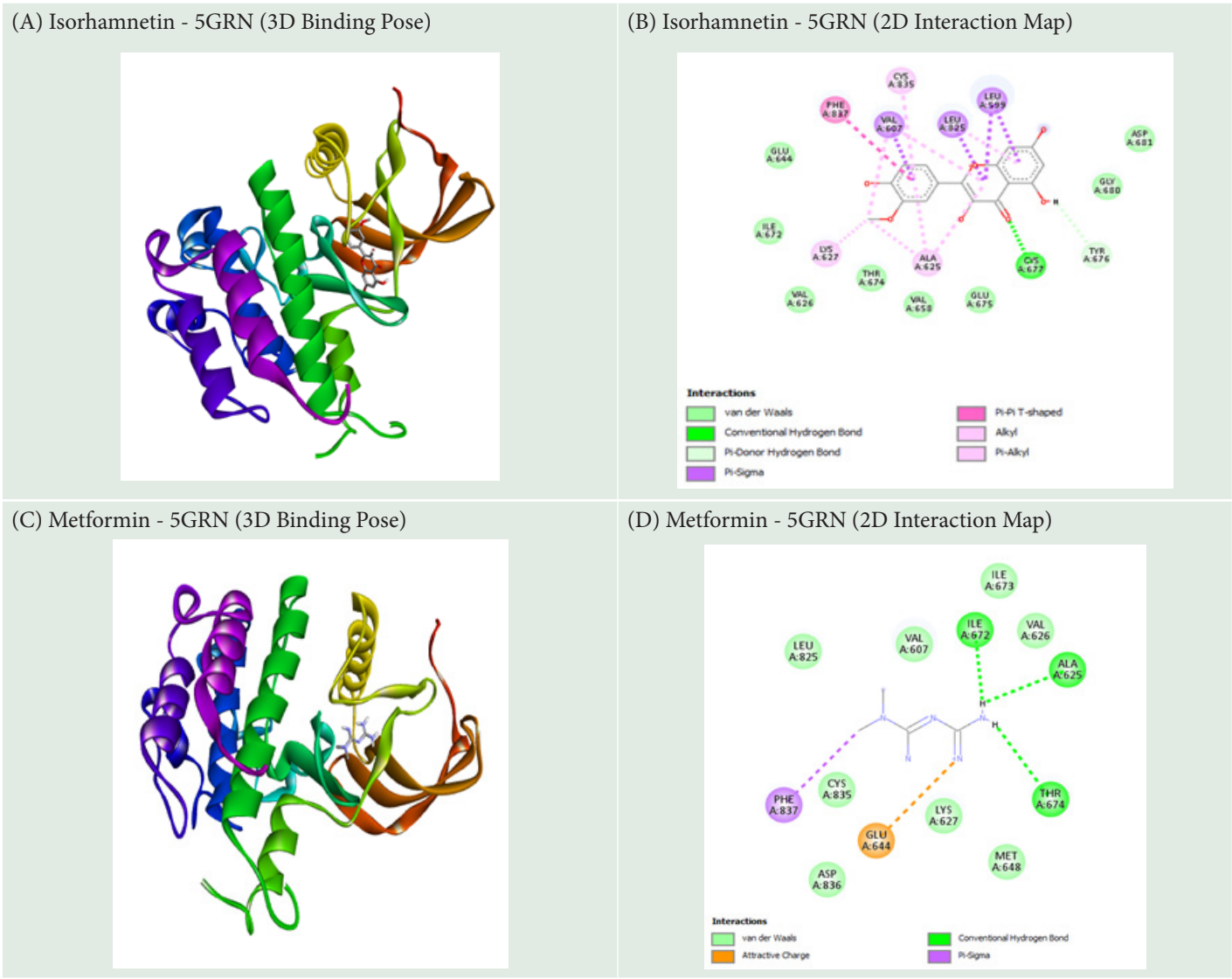


Figure 4: Comparative molecular docking analysis of isorhamnetin and metformin within the 5GRN binding pocket. (A) Three-dimensional binding conformation of isorhamnetin (-10.0 kcal/mol), (B) corresponding 2D protein-ligand interaction map, (C) three-dimensional binding conformation of metformin (-5.0 kcal/mol), and (D) corresponding 2D protein-ligand interaction map.

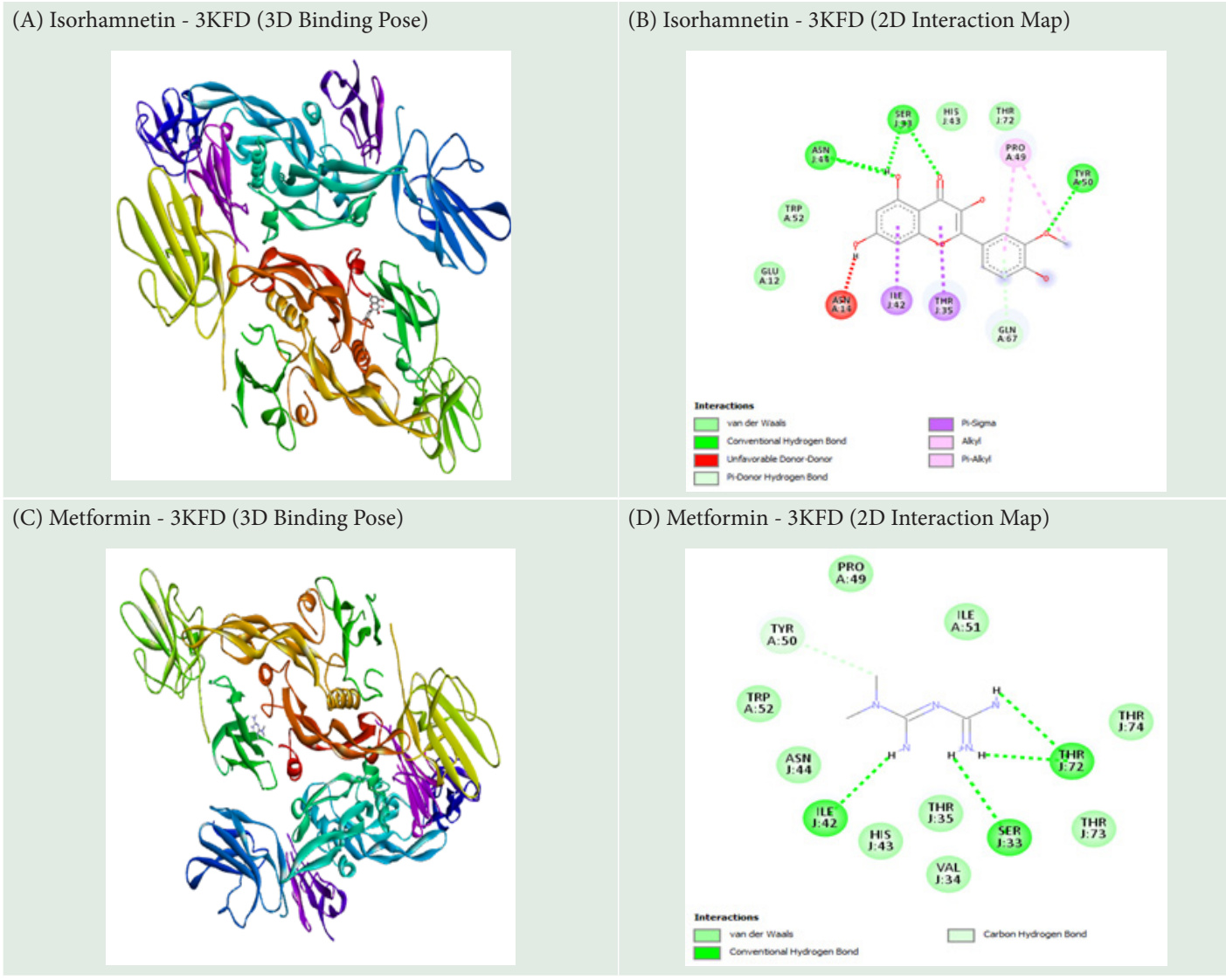


Figure 5: Docking poses and interaction profiles of isorhamnetin and metformin with TGF-β1 (3KFD). (A) 3D binding pose of isorhamnetin, (B) 2D interaction map of isorhamnetin, (C) 3D binding pose of metformin, and (D) 2D interaction map of metformin, showing binding affinities of -8.4 kcal/mol and -5.5 kcal/mol.

Table 3: Superoxide radical scavenging (SOD-like) activity of *Petroselinum crispum* methanolic extract and ascorbic acid.

Sl. No.	Concentration (µg/mL)	Control Absorbance	%RSA (Standard)	%RSA (Test)
1.	10	0.86	12.50	10.33
2.	20	0.86	21.25	17.55
3.	40	0.86	32.50	26.88
4.	60	0.86	46.25	40.30
5.	80	0.86	61.88	59.88
6.	100	0.86	70.00	68.25
IC_{50} Values				
	Sample		IC_{50} (µg/mL)	
	Standard		65.94	
	Test extract		70.98	

Abbreviations: SOD, superoxide dismutase; RSA, radical scavenging activity; IC_{50}, concentration required to inhibit 50% of superoxide radicals.

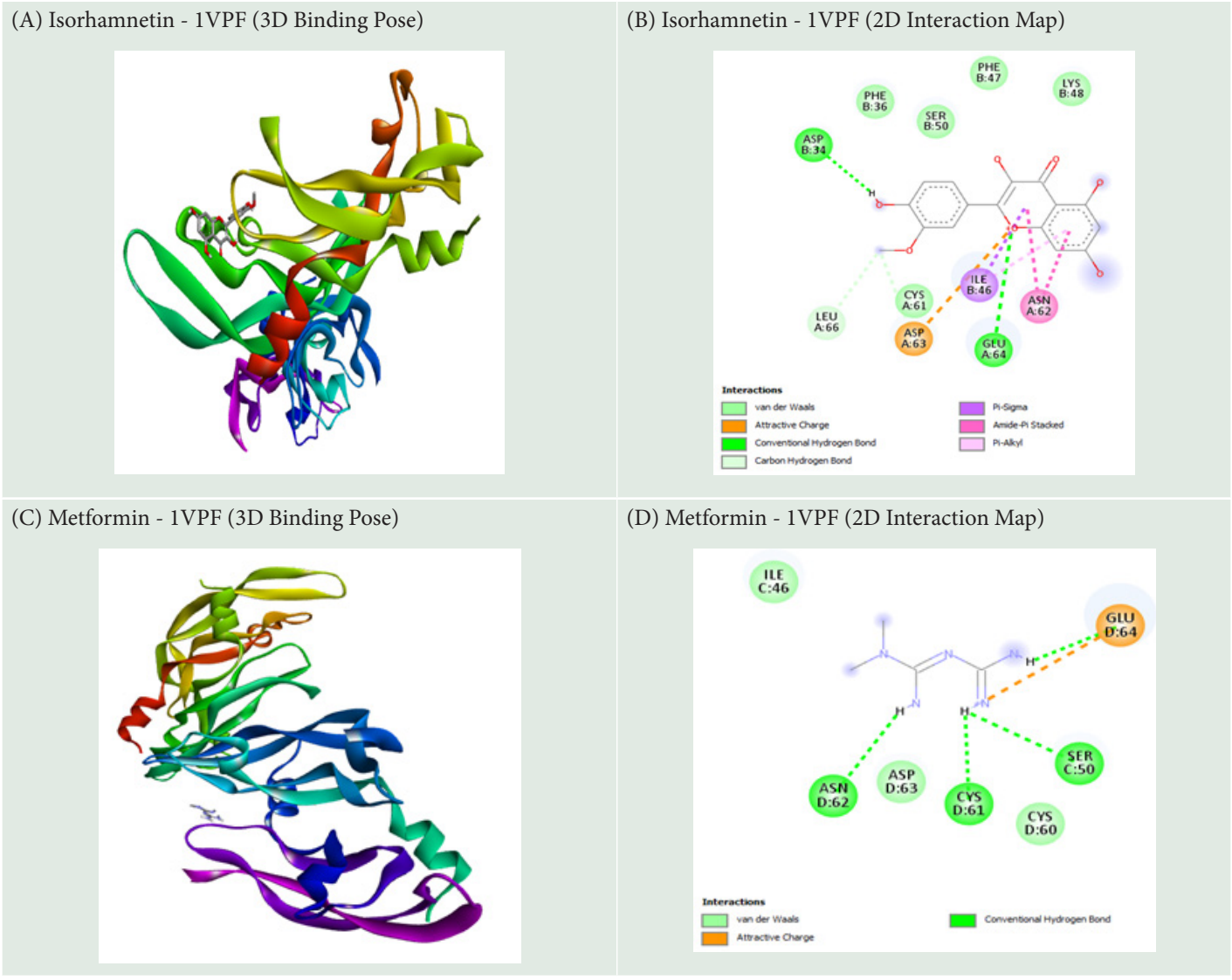


Figure 6: Comparative molecular docking analysis of isorhamnetin and metformin within the 1VPF binding pocket. (A) Three-dimensional binding conformation of isorhamnetin (-7.4 kcal/mol), (B) corresponding 2D protein-ligand interaction map, (C) three-dimensional binding conformation of metformin (-4.9 kcal/mol), and (D) corresponding 2D protein-ligand interaction map.

(-9.2 kcal/mol), suggesting potential cross-talk among growth factor-mediated signaling pathways involved in diabetic wound healing. Protein-protein docking results are presented in Table 6. The protein-protein docking interactions of becaplermin with PDGFR-β, VEGF-A, and TGF-β1 are illustrated in Figure 9, demonstrating the structural basis of growth factor-mediated signaling involved in fibroblast proliferation, angiogenesis, and extracellular matrix remodeling during diabetic wound healing.

DISCUSSION

Delayed wound healing is a major problem in diabetes mellitus and is mainly due to inflammation, oxidative stress, impaired angiogenesis, and reduced fibroblast activity. Antioxidant therapy that modulates oxidative stress and growth factor signaling pathways can be therapeutically helpful for diabetic wounds (Yadav *et al.*, 2025). In this study, we examined the antioxidant potential of *Petroselinum crispum* extract and the molecular interaction of isorhamnetin, the dominant flavonoid constituent of the extract, and its role in wound healing. The antioxidant assays showed that *P. crispum* extract has free radical scavenging activity (Mohanasundaram *et al.*, 2023). While IC_{50} was slightly higher in the extract than ascorbic acid in the DPPH and superoxide radical scavenging assays, the extract still remains biologically relevant (Wang *et al.*, 2025). Flavonoids and phenolics in *P. crispum* may play a large role in this activity. It is known that flavonoids, like isorhamnetin, are highly antioxidant in nature as they can donate hydrogen to reactive oxygen species and stabilize them (Chen *et al.*, 2023). The hydroxyl groups in their structure help to transfer electrons to the free radicals to remove them. In diabetic wounds, excessive production of reactive oxygen species can lead to damage of cells and reduce fibroblast proliferation and collagen deposition. Therefore, antioxidants that reduce oxidative stress should help heal the wounds from the inflammatory stage to the

Table 4: Molecular docking scores of isorhamnetin and metformin against diabetic wound-healing target proteins.

Target Protein	PDB ID	Biological Role in Wound Healing	Isorhamnetin Binding Energy (kcal/mol)	Metformin Binding Energy (kcal/mol)	Key Interacting Residues	Interaction Type
PDGF-BB	1PDG	Fibroblast proliferation and collagen deposition	-6.6	-4.5	Lys62, Glu64, Arg27, Val89	H-bond, hydrophobic, electrostatic
PDGFR-β	5GRN	Cell migration and angiogenesis	-10.0	-5.0	Asp850, Lys634, Tyr751, Phe845	H-bond, π-π stacking, hydrophobic
TGF-β1	3KFD	ECM remodeling and fibrosis regulation	-8.4	-5.5	Arg25, Ser47, Tyr39, Leu42	H-bond, hydrophobic
VEGF-A	1VPF	Angiogenesis and vascular regeneration	-7.4	-4.9	Lys48, Asp63, Ile46, Phe36	H-bond, hydrophobic
MMP-9	1GKC	Extracellular matrix degradation	-8.8	-6.3	His401, Glu402, Tyr423, Zn^{2+}	H-bond, metal coordination
Nrf2	4ZY3	Antioxidant defense and oxidative stress regulation	-9.6	-5.6	Arg499, Phe490, Asn482, Val512	H-bond, hydrophobic, π-π interaction

Abbreviations: PDGF-BB, platelet-derived growth factor-BB; PDGFR-β, platelet-derived growth factor receptor beta; TGF-β1, transforming growth factor-beta 1; VEGF-A, vascular endothelial growth factor A; MMP-9, matrix metalloproteinase-9; Nrf2, nuclear factor erythroid 2-related factor 2.

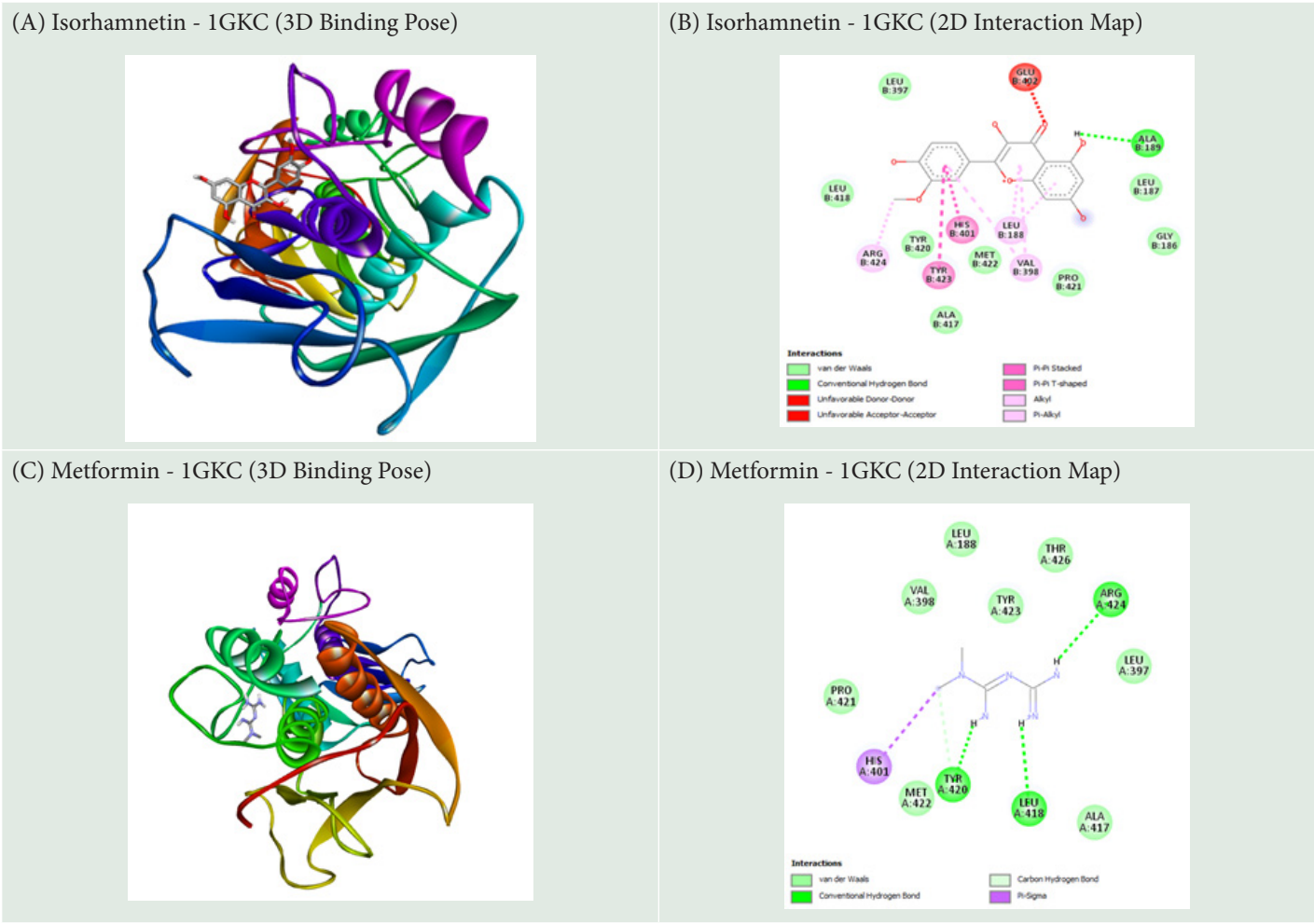


Figure 7: Docking poses and interaction maps of isorhamnetin and metformin in the 1GKC binding pocket. (A) Isorhamnetin - 1GKC (3D Binding Pose) (B) Isorhamnetin - 1GKC (2D Interaction Map) (C) Metformin - 1GKC (3D Binding Pose) (D) Metformin - 1GKC (2D Interaction Map). Binding energies were -8.8 and -6.3 kcal/mol, respectively.

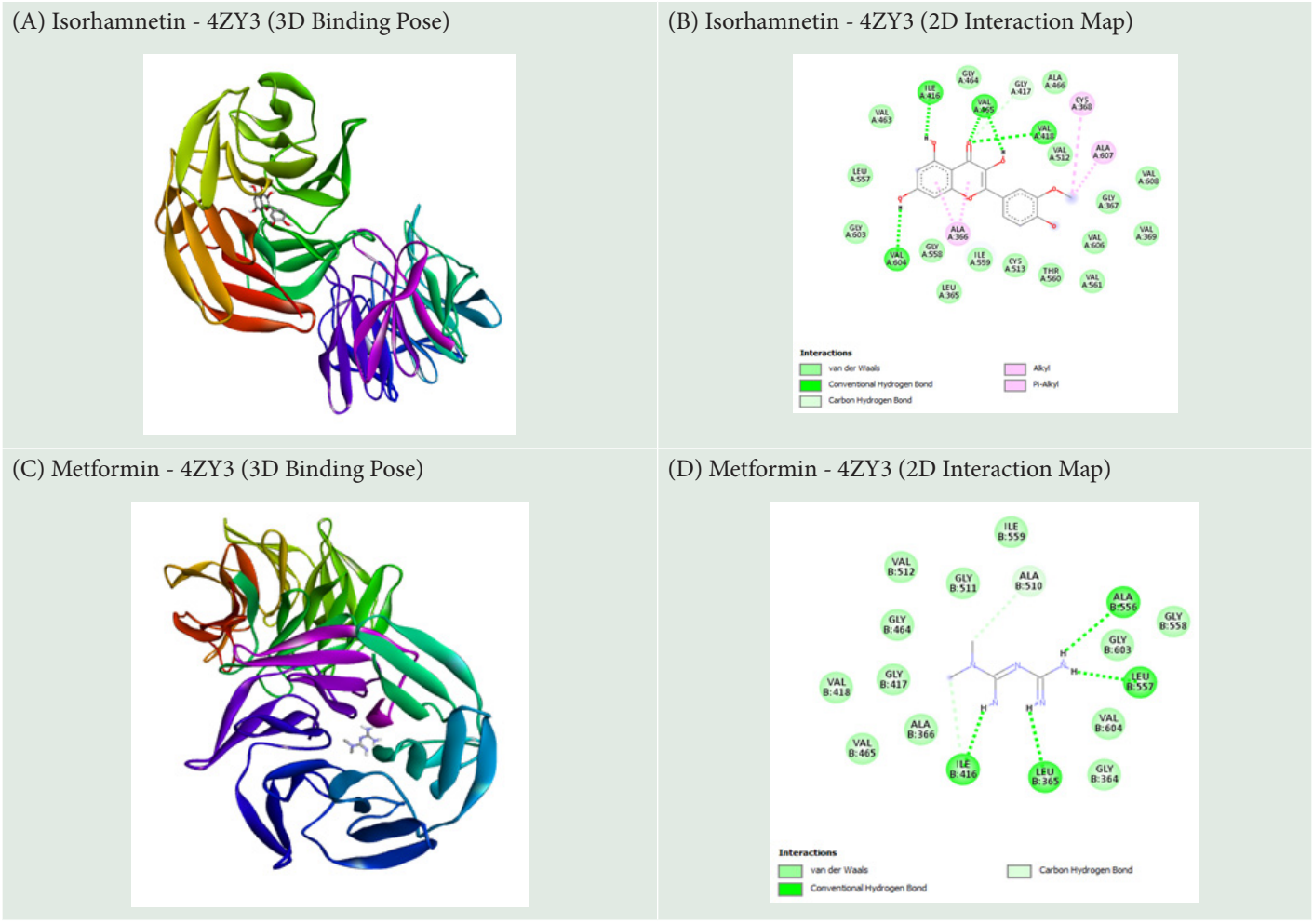


Figure 8: Comparative molecular docking analysis of isorhamnetin and metformin within the 4ZY3 binding pocket. (A) Isorhamnetin - 4ZY3 (3D Binding Pose) (B) Isorhamnetin - 4ZY3 (2D Interaction Map) (C) Metformin - 4ZY3 (3D Binding Pose) (D) Metformin - 4ZY3 (2D Interaction Map).

Table 5: Comparative molecular docking analysis of isorhamnetin, metformin, and becaplermin against diabetic wound-healing targets.

Compound	Best Target	Binding Energy (kcal/mol)	Mechanistic Implication
Isorhamnetin	PDGFR-β	-10.0	Promotes fibroblast proliferation and angiogenesis
Metformin	PDGFR-β	-5.0	Moderate receptor interaction
Becaplermin	PDGFR-β	-13.4	Direct growth factor receptor activation

Abbreviations: PDGFR-β, platelet-derived growth factor receptor beta.

Table 6: Protein-protein docking analysis of becaplermin with major wound healing-related growth factor receptors and signaling proteins.

Protein Complex	PDB ID (Receptor)	Binding Energy (kcal/mol)	Interface Area (Å^2)	Hydrogen Bonds	Salt Bridges	Functional Implication
Becaplermin - PDGFR-β	5GRN	-13.4	1840	16	5	Strong receptor activation and fibroblast proliferation
Becaplermin - VEGF-A	1VPF	-10.1	1325	11	3	Angiogenic signaling cross-talk
Becaplermin - TGF-β1	3KFD	-9.2	1190	9	2	ECM remodeling modulation

Abbreviations: PDGFR-β, platelet-derived growth factor receptor beta; VEGF-A, vascular endothelial growth factor A; TGF-β1, transforming growth factor-beta 1; Å^2, square angstrom.

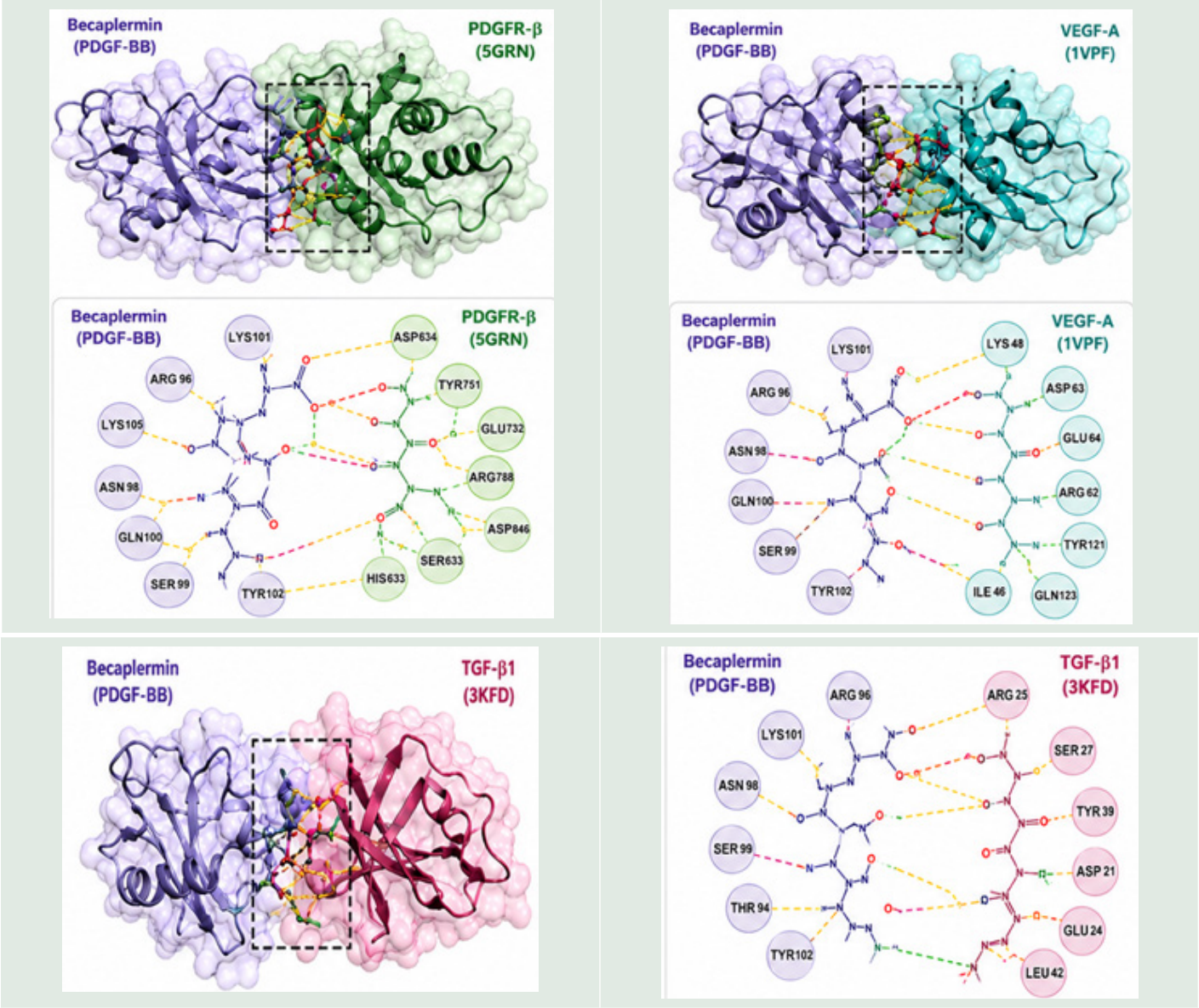


Figure 9: Protein-protein docking interactions of becaplermin with wound healing-related targets. (A) PDGFR-β (5GRN; -13.4 kcal/mol), (B) VEGF-A (1VPF; -10.1 kcal/mol), and (C) TGF-β1 (3KFD; -9.2 kcal/mol). The upper panel shows the 3D docking conformation, while the lower panel illustrates the corresponding 2D interaction map.

proliferative one. Molecular docking analysis also shed further light on the potential molecular mechanisms for isorhamnetin to promote wound healing. The strongest binding was observed with PDGFR-β, a receptor tyrosine kinase involved in fibroblast proliferation and migration (Herman and Herman, 2023; Lu *et al.*, 2025).

PDGFR signaling promotes granulation tissue formation and collagen production, which are important for tissue repair. The strong interaction between isorhamnetin and PDGFR-β suggests that it can be used to increase fibroblast activity and promote extracellular matrix formation in the diabetic wound, which is of particular importance in diabetic wounds where fibroblast dysfunction often results in impaired tissue regeneration (Han *et al.*, 2025; Yadav, 2023). Another important finding was the strong binding of isorhamnetin to Nrf2. Nrf2 is an important transcription factor responsible for the production of antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase. Activation of the Nrf2 signaling pathway enhances the cell's defense against oxidative stress. The interaction between isorhamnetin and Nrf2 implies that isorhamnetin could activate endogenous antioxidant enzymes in the wound tissue and hence protect the wound tissue against oxidative damage (Porwal *et al.*, 2025; Sahu *et al.*, 2025; Wang *et al.*, 2025).

This is consistent with the antioxidant activity exhibited in the *in vitro* analyses. MMP-9 mediated interaction is also of great mechanistic interest. Matrix metalloproteinases are involved in the remodeling of the extracellular matrix in the wound. However, excessive MMP-9 activity in diabetic wounds may

lead to degradation of structural proteins and slow tissue repair (Miricescu *et al.*, 2021). The interaction between isorhamnetin and MMP-9 suggests that the molecule may play a role in matrix remodeling (Sun and Shahrajabian, 2023; Yuan *et al.*, 2024). The molecule was also found to have mild binding affinity with VEGF-A and TGF-β1, which are important for angiogenesis and extracellular matrix deposition. VEGF-A promotes new blood vessels to supply oxygen and nutrients to the regenerating tissues (Fu *et al.*, 2022; Guo *et al.*, 2023).

TGF-β1 is responsible for fibroblast differentiation and collagen synthesis, which are involved in wound contraction and tissue remodeling. The docking analysis with metformin showed that metformin had a lower affinity for the molecular pathways involved in wound healing compared to isorhamnetin. Whereas metformin primarily improves wound healing through glycemic control, plant-based compounds such as isorhamnetin might exert more direct effects on cellular signaling pathways involved in tissue regeneration (Qnais *et al.*, 2025).

The docking analysis of becaplermin further highlights the importance of PDGF signaling in wound healing. Becaplermin has a strong interaction with PDGFR-β, supporting its established clinical use in the treatment of diabetic foot ulcers (Embil and Nagai, 2002). The additional interactions with VEGF-A and TGF-β1 also suggest that PDGF signaling is involved in angiogenic and extracellular matrix remodeling pathways for tissue repair. Taken together, the findings of this study suggest that isorhamnetin may play a role in diabetic wound healing due to its antioxidant activity, fibroblast proliferation, angiogenesis, and extracellular matrix remodeling. The integration of *in vitro* antioxidant assays with *in silico* molecular docking studies has provided insight into the therapeutic potential of isorhamnetin and further study of *Petroselinum crispum* as a natural source of wound healing agents is encouraged (Kong *et al.*, 2009; Nouioura *et al.*, 2024; Wang and Yang, 2024).

CONCLUSION

We investigated the antioxidant activity of *Petroselinum crispum* extract and the interaction of the major flavonoid component isorhamnetin with the proteins involved in diabetic wound healing. *In vitro* antioxidant assays demonstrated that the extract has great free radical scavenging activities and that it was effective in DPPH and superoxide radical scavenging assays. While its antioxidant activity was a little lower than that of the standard ascorbic acid extract, the relatively similar IC_{50} indicates that it is a bioactive phytochemical molecule with the ability to neutralize reactive oxygen species. This antioxidant profile is of particular relevance in diabetic wounds where excessive oxidative stress is the main cause of delay in tissue repair and regeneration. Molecular docking analysis of the molecule revealed the potential therapeutic value of isorhamnetin in wound healing. The molecule exhibited strong binding affinity toward several key proteins involved in tissue regeneration, including PDGFR-β, Nrf2, and MMP-9, and may have contributed to fibroblast proliferation and collagen formation, which are key for granulation tissue formation. Interaction with Nrf2 indicates that endogenous antioxidant defense mechanisms are activated, while binding to MMP-9 suggests a regulatory role in extracellular matrix remodeling. Moderate interactions with VEGF-A and TGF-β1 further imply possible involvement in angiogenesis and collagen deposition during wound healing. In comparison with metformin, the docking of isorhamnetin showed comparatively weaker binding interactions at some molecular targets that are integral for wound repair. Protein-protein docking of becaplermin confirmed strong interaction with PDGFR-β, further supporting the significance of PDGF signaling in diabetic wound healing. Overall, the integration of *in vitro* antioxidant assessment and *in silico* molecular docking study of isorhamnetin showed promising therapeutic potential for diabetic wound healing.

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ABBREVIATIONS

ROS: Reactive Oxygen Species; **PDGF:** Platelet-Derived Growth Factor; **PDGFR:** Platelet-Derived Growth Factor Receptor; **VEGF:** Vascular Endothelial Growth Factor; **TGF-β:** Transforming Growth Factor Beta; **MMP:** Matrix Metalloproteinase; **Nrf2:** Nuclear Factor Erythroid 2-Related Factor 2; **DPPH:** 2,2-Diphenyl-1-picrylhydrazyl; **SOD:** Superoxide Dismutase; **NBT:** Nitro Blue Tetrazolium; **EDTA:** Ethylenediaminetetraacetic Acid; **ECM:** Extracellular Matrix; **PDB:** Protein Data Bank.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Ashish Kumar Nirmal conceived the study, conducted the experiments, analyzed the data, and drafted the manuscript. **Ashish Singhai** supervised the study, interpreted the data, and critically revised the manuscript. **Mukesh Singh Sikarwar** contributed to study design, data interpretation, and manuscript editing. All authors approved the final manuscript.

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