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An In Silico Docking Study of Guava (Psidium guajava L.) Phytochemicals with Angiogenesis and Antimicrobial Targets in Diabetic Wound Healing

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Abstract

This study explores the potential of Guava (Psidium guajava L.) phytochemicals in promoting diabetic wound healing through in silico screening of their angiogenic and antimicrobial activities. The research focuses on identifying bioactive compounds capable of interacting with key protein targets that are involved in wound repair and infection control. Phytochemicals retrieved from guava were evaluated for their pharmacokinetic and toxicity properties using the software SwissADME and ProTox-II, where compounds meeting Lipinski's Rule of Five and showing favorable dermal permeability (logKp > -8.0) were selected for docking. Molecular Docking simulations were performed via PyRx to assess binding affinities between guava compounds and selected target proteins, followed by RMSD validation to confirm docking accuracy. Post-docking analysis using PyMOL revealed key interactions including hydrogen bonds and hydrophobic contacts with crucial amino acid residues, highlighting stable compound-target binding. Overall, results suggest that guava-derived phytochemicals possess promising dual-action properties, providing a natural, cost-effective candidate for future diabetic wound healing properties.

Keywords: Guava (Psidium guajava L.), molecular docking, angiogenesis, antimicrobial activity, diabetic wound healing, PyRx.

Introduction

Diabetes Mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia caused by defects in insulin production or utilization. It was classified into two main types: Type 1 Diabetes (T1DM), which resulted from autoimmune destruction of pancreatic beta cells, and Type 2 Diabetes (T2DM), which occurred due to insulin resistance and insufficient insulin production [21]. Globally, diabetes posed a growing public health burden, with an estimated 537 million adults affected in 2021, disproportionately impacting low- and middle-income countries such as the Philippines [23]. One of its serious complications was impaired wound healing, which leads to chronic ulcers, severe infections, and amputations when untreated [1].

Chronic hyperglycemia induced oxidative stress, damaged blood vessels and nerves, and weakened immune responses, all of which disrupted angiogenesis and tissue regeneration [4][10]. Insulin, the gold standard treatment, had been reported to enhance keratinocyte migration, angiogenesis, and collagen deposition, and served as the benchmark for this study. Guava (*Psidium guajava L.*) had long been recognized in traditional medicine for its phytoconstituents with antioxidant, antimicrobial, and anti-inflammatory activities [16]. Phytochemicals such as quercetin, catechin, gallic acid, and kaempferol had been reported to modulate wound healing pathways and exhibit antibacterial effects against pathogenic strains [17][18]. However, comprehensive in silico evaluation of these compounds against both angiogenesis-related receptors and antimicrobial protein targets remained limited.

This study, therefore, introduced GuavaHeal, an in silico investigation of *P. guajava* phytochemicals using molecular docking, ADME prediction, and toxicity profiling. Computational platforms including SwissADME, ProTox-II, AutoDock Vina, and Cytoscape were utilized to evaluate absorption, safety, receptor binding affinity, and potential mechanisms of action [6][2][24]. By integrating pharmacokinetic modeling and docking analysis, this research aimed to identify guava-derived compounds with dual angiogenic and antimicrobial potential for diabetic wound healing using a cost-effective and sustainable framework.

Research Questions

This study on guava (*Psidium guajava L.*) serum in promoting wound healing under diabetic conditions will answer the following questions:

1. How do guava (*Psidium guajava* L.) phytochemicals interact with wound-healing proteins under diabetic conditions based on in silico molecular docking?
2. What are the predicted antimicrobial and anti-inflammatory effects of guava phytochemicals against common diabetic wound pathogens using computational tools?
3. How does the efficacy of guava compounds compare to insulin as a benchmark standard in terms of predicted binding affinities, ADME profiles, and toxicity assessments?

Review of Related Literature

This review explored the properties of *Psidium guajava* L. (guava), including its bioactive compounds, health benefits, and healing properties. This study evaluated the effectiveness of guava phytochemicals in promoting wound healing under diabetic conditions by using in silico methods to predict their interactions with wound-healing proteins, their roles in tissue regeneration, and their potential mechanisms of action.

Type 2 Diabetes

Type 2 diabetes mellitus (T2DM) affected over 460 million people worldwide and may exceed 700 million by 2045. It is a long-term condition where the body has high blood sugar and does not respond well to insulin, which often slows down wound healing. Diabetes complications were primarily due to reduced blood flow, diabetic neuropathy, and oxidative stress—factors that disrupt tissue repair and promote chronic, non-healing ulcers [5].

Phytochemicals & Biological Properties of Guava

Guava (*Psidium guajava*) is a medicinal plant that had been used for a long time to treat various

illnesses [7]. It is rich in dietary fiber, protein, vitamins A and C, and essential minerals, and contains important compounds like flavonoids, tannins, alkaloids, and phenolic compounds [16][11][25]. These components give guava many health benefits, including antioxidant, anti-inflammatory, and antimicrobial properties, as well as helping control blood sugar [13][12].

In Silico

In silico tools predicted how guava bioactives interact with key wound-healing proteins such as VEGF, TGF-β1, and IL-6. Molecular docking with AutoDock Vina estimated binding affinities of quercetin, catechin, and gallic acid, while SwissADME predicted dermal absorption, lipophilicity, and drug-likeness. ProTox-II classified compounds based on their potential toxicity and LD_{50} values, providing an early safety assessment [6][2][15]. These computational results complemented *in vitro* findings and reduced the need for invasive *in vivo* studies.

Molecular Docking

Molecular docking is an *in silico* method used to predict how small molecules fit into the binding sites of target proteins. It estimates the strength of interaction through binding energy values, where lower energies indicate stronger and more stable binding [24][15]. This approach allowed guava phytochemicals to be screened for potential wound-healing and antimicrobial effects without the need for immediate laboratory testing.

Insulin and Wound Healing

Insulin played a dual role as both a glucose regulator and a wound-healing agent. Studies showed that insulin accelerates keratinocyte migration, stimulates fibroblast proliferation, and enhances angiogenesis through activation of AKT and ERK signaling pathways [14]. It has also been demonstrated to reduce inflammation and promote collagen deposition, thereby expediting tissue regeneration in diabetic wounds [22]. Clinical applications of topical and systemic insulin therapies highlight its potential as a comparator drug, making it a reliable benchmark standard in evaluating the predicted wound-healing efficacy of guava phytochemicals *in silico*.

ADME and Toxicity Evaluation

SwissADME was used to predict key pharmacokinetic properties such as lipophilicity, molecular weight, topological polar surface area (TPSA), and skin permeability. Compounds that satisfied Lipinski's Rule of Five and showed favorable dermal absorption were prioritized [6]. ProTox-II complemented this by predicting toxicity classifications, LD_{50}, and organ-specific risks [2], ensuring that selected guava phytochemicals were safe for further docking studies.

Docking Affinity Analysis

AutoDock Vina estimated binding affinities of guava phytochemicals with wound-healing and antimicrobial targets. Ligand efficiency was calculated to normalize results, while re-docking of co-crystal ligands (RMSD ≤ 2.0 Å) confirmed accuracy [24][15]. Stronger binding compounds were identified and compared through bar graph visualization.

Interaction Profiling and Integrative Analysis

Post-docking visualization with PyMOL and Discovery Studio identified key interactions such as hydrogen bonds, hydrophobic contacts, and π–π stacking. These findings, along with docking affinities and ADME/Tox profiles, were integrated into compound–target networks using Cytoscape. Heatmaps and interaction maps highlighted multi-target guava phytochemicals, revealing their potential to promote angiogenesis, provide antimicrobial defense, and ensure safety [15][3].

Methods

This study will be conducted in six phases: (1) Compound Collection and Preparation, (2) ADME and Toxicity Prediction, (3) Protein Target Preparation, (4) Molecular Docking, (5) Post-Docking Interaction Analysis, and (6) Integrative Analysis. The procedures describe the computational tools and datasets used so that the experiment can be replicated by other researchers.

Phase 1: Compound Collection and Preparation

Phytochemicals from guava, including quercetin, catechin, gallic acid, kaempferol, isoquercetin, and naringenin, were retrieved from the PubChem database in 3D SDF format. The structures were converted to .pdb format using Open Babel while preserving 3D coordinates. AutoDock Tools was then used to assign rotatable bonds and Gasteiger charges, and the ligands were saved in .pdbqt format for molecular docking.

Phase 2: ADME and Toxicity Prediction

In silico pharmacokinetic and toxicity screening was performed using SwissADME and ProTox-II. Parameters such as molecular weight, lipophilicity (logP), topological polar surface area (TPSA), skin permeation (logKp), toxicity class, and LD_{50} were predicted. Compounds with high toxicity (ProTox class ≤ 3) or poor permeability (logKp < –8.0) were excluded. The remaining compounds were summarized and analyzed using descriptive statistics and graphical representations.

Phase 3: Protein Target Preparation

Protein targets related to angiogenesis (VEGFR2, FGFR1, TGF-βR1, IL-6R) and antimicrobial activity (MurA, DNA gyrase, and penicillin-binding protein) were obtained from the Protein Data Bank. Structures were cleaned in PyMOL by removing water molecules and non-essential ligands. Polar hydrogens and Gasteiger charges were added in PyRx, and receptors were saved in .pdbqt format. Binding sites were defined using known active-site coordinates or co-crystallized ligands.

Phase 4: Molecular Docking

Docking simulations were conducted using AutoDock Vina. Configuration files containing receptor and ligand files, grid center, and box dimensions were prepared for each ligand–receptor pair. Docking was run with an exhaustiveness value of 8 and nine binding modes. Redocking of co-crystal ligands was performed to validate the setup (RMSD ≤ 2.0 Å). Binding affinities and ligand poses were compiled and compared using tables and bar graphs.

Phase 5: Post-Docking Interaction Analysis

The best docking poses were analyzed using PyMOL and Discovery Studio to identify hydrogen bonds, hydrophobic interactions, and key binding residues. Binding energies were normalized using ligand efficiency to compare compounds of different sizes. Results were presented in tables, heatmaps, and bar graphs.

Phase 6: Integrative Analysis

Docking results, ADME predictions, toxicity data, and interaction analyses were integrated into a comprehensive dataset. Cytoscape was used to construct compound–target interaction networks illustrating the potential mechanisms of guava phytochemicals in wound healing, particularly through angiogenesis and antimicrobial activity. Findings were summarized using tables, charts, and network diagrams.

Results

This section presents the major findings of the study. Results are discussed in the context of research questions and objectives. The study aimed to determine the pharmacological potential of guava (*Psidium guajava* L.) phytochemicals—Catechin, Kaempferol, Naringenin, and Gallic Acid—against six target proteins: DNA gyrase, FGFR1, IL-6R, PBP, TGF-β, and VEGFR.

Lipinski Drug-Likeness and ADME Evaluation

All tested ligands complied with Lipinski's Rule of Five except Isoquercetin and Rutin, as shown in *Table 1*. Compounds with zero violations (Catechin, Kaempferol, Naringenin, and Gallic Acid) displayed high gastrointestinal absorption and non-permeability to the blood–brain barrier. Skin permeability ranged from –5.88 to –7.82 cm/s, indicating moderate transdermal diffusion suitable for topical use.

Table 1: Physicochemical and Drug-Likeness Properties of Guava Phytochemical

Molecule	Mw (G/mol)	Ilogp	Tpsa (Å²)	Gi Absorption	Bbb Permeant	Log Kp (Cm/s)	Lipinski Violations	Evaluation
Gallic Acid	170.12	0.06	97.99	High	No	-6.59	0	Accepted
Catechin	290.27	1.13	110.38	High	No	-7.82	0	Accepted
Naringenin	270.24	1.73	90.9	High	No	-5.88	0	Accepted
Quercetin	302.24	1.63	131.36	High	No	-7.05	0	Accepted
Isoquercetin	434.35	0.89	190.28	Low	No	-7.58	2	Moderately Accepted
Rutin	596.49	1.68	269.43	Low	No	-10.09	3	Not Accepted
Kaempferol	286.24	1.76	111.13	High	No	-6.7	0	Accepted

Toxicity and Cytotoxicity Evaluation

Toxicity profiling results (*Table 2*) revealed that Catechin was the safest compound with an LD_{50} of 10 000 mg/kg (Toxicity Class 6). Naringenin and Gallic Acid were low-toxic (Class 4), while Kaempferol was moderately safe (Class 5). All were non-cytotoxic, confirming suitability for drug development.

Table 2 : Predicted Toxicity and Cytotoxicity Profiles of Selected Compounds

Molecule	Ld50 (Mg/kg)	Toxicity Class	Cytotoxicity	Safety Evaluation
Gallic Acid	2000	4	Inactive (low toxicity)	Moderately Safe
Catechin	10000	6	Inactive (non-toxic)	Very Safe
Naringenin	2000	4	Inactive (low toxicity)	Moderately Safe
Quercetin	159	3	Active (cytotoxic)	Caution / Less Safe
Isoquercetin	5000	5	Inactive (moderate)	Moderately Safe
Rutin	5000	5	Inactive (moderate)	Moderately Safe
Kaempferol	3919	5	Inactive (moderate)	Moderately Safe

Molecular Docking Binding Affinity

Binding affinities of the compounds toward the six receptors are summarized in *Table 3*. Values ranged from –5.1 kcal/mol to –9.5 kcal/mol, where Naringenin–TGF-β (–9.5 kcal/mol) showed the strongest interaction, followed by Catechin–VEGFR (–8.8 kcal/mol) and Kaempferol–FGFR1 (–8.6 kcal/mol).

Table 3 : Binding Affinity of Guava Phytochemicals with Target Proteins

Protein Target	Best Ligand	Binding Affinity (Kcal/mol)	Rank	Remarks
DNA gyrase	Catechin	-7.6	1st	Good binding
FGFR1	Kaempferol	-8.6	1st	Strongest binding
IL-6R	Naringenin	-6	1st	Moderate binding
PBP	Catechin	-7.5	1st	Good binding
TGF-β	Naringenin	-9.5	1st	Strongest binding
VEGFR	Catechin	-8.8	1st	Strongest binding

3.1.4. Post Docking Interaction Analysis

Hydrogen-bond and hydrophobic interactions were analyzed to assess complex stability (*Table 4*). Catechin formed 3 H-bonds with DNA gyrase (ASP641, GLU531, ALA564) stabilized by π-cation and π-sigma interactions; Kaempferol–FGFR1 established 3 H-bonds (GLU562, ASP641, ALA512) and π-π stacking; Naringenin–TGF-β formed 2 H-bonds (ASP269, THR272) with hydrophobic TRP273, GLY271; and Catechin–VEGFR showed 3 H-bonds (GLU883, ALA864, LYS868) with π-π stacking, indicating strong receptor anchoring.

Table 4 : Hydrogen-Bond and Hydrophobic Interaction Analysis of Best Docked Complexes

Compound	Target Protein	No. Of H-bonds	H-bond Residues	Hydrophobic Residues	π–π / π–Cation Interactions	Key Residues Involved	Interaction Summary
Catechin	DNA gyrase	3	ASP641, GLU531, ALA564	MET535, LEU630, TYR563, VAL512, GLY567	π–cation, π–sigma	MET535, LEU630	Stable polar–aromatic network
Kaempferol	FGFR1	3	GLU562, ASP641, ALA512	PHE642, LEU644, VAL559, ILE545, LEU630	π–π stacking	PHE642, LEU644	Aromatic stacking in active pocket
Naringenin	IL-6R	3	GLU144, ASN226, GLN158	PRO145, SER227	—	GLU144, ASN226	Polar compact fit via van der Waals surface
Catechin	PBP	3	GLU239, SER240, ARG241	ARG151, THR165, VAL277	—	ARG151, THR165	Electrostatic and H-bond stabilization
Naringenin	TGF-β	2	ASP269, THR272	TRP273, GLY271, HOH716	—	TRP273, GLY271	Water-mediated H-bonds; stable binding
Catechin	VEGFR	3	GLU883, ALA864, LYS868	VAL913, HIS1024, CYS919, ALA866	π–π T-shaped	HIS1024, VAL913	Strong aromatic and halogen interactions

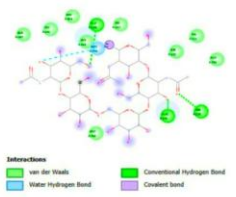

Figure 7: Dna Gyrase and Catechin

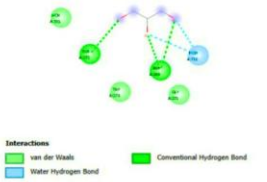

Figure 8: FGFR1 and Kaempferol

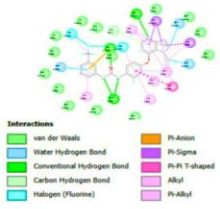

Figure 9: IL-6R and Naringenin

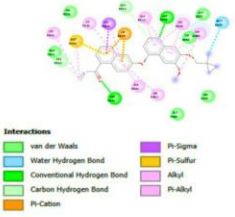

Figure 10: PBP and Catechin

Figure 11. TGF-βR1 and Naringenin

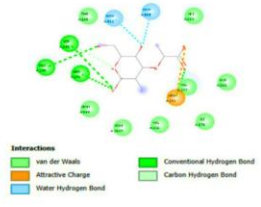

Figure 12. VEGFR2 and Catechin

Ligand Efficiency and RMSD Validation

Ligand-efficiency and RMSD validation results are presented in *Table 5*. Efficiency values ranged from –0.30 to –0.475, with Naringenin–TGF-β (–0.475) as the most efficient. RMSD values (0.000–1.966 Å) were below the 2 Å threshold, confirming docking accuracy.

Table 5. Validation of Docking Results Based on Ligand Efficiency and RMSD

Receptor	Best Ligand	Binding Energy	No. Of Heavy Atoms	Ligand Efficiency	Rmsd
DNA_gyrase	Catechin	-7.6	21	-0.362	0.000Å
FGR1	Kaempferol	-8.6	21	-0.409	0.000Å
IL-6R	Naringenin	-6	20	-0.3	0.000Å
PBP	Catechin	-7.5	21	-0.357	0.000Å
TGF	Naringenin	-9.5	20	-0.475	1.966Å
VEGFR	Catechin	-8.8	21	-0.419	0.000Å

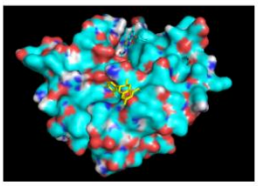

Figure 1: DNA Gyrase and Catechin

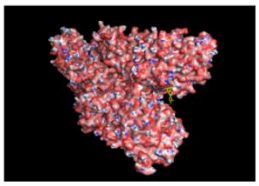

Figure 2: FGFR1 and Kaempferol

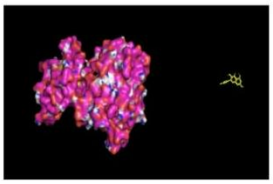

Figure 3: IL-6R and Naringenin

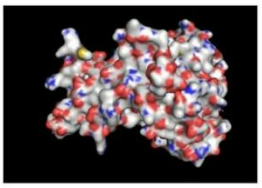

Figure 4: PBP and Catechin

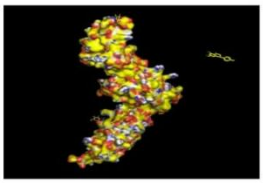

Figure 5: TGF-βR1 and Naringenin

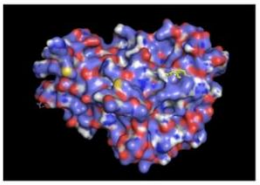

Figure 6: VEGFR2 and Catechin

Discussion

The results obtained from the computational analyses were evaluated and interpreted based on binding stability, pharmacokinetic properties, and toxicity profiles of the tested ligands.

ADME and Drug-Likeness Evaluation

All compounds except Isoquercetin and Rutin passed the Lipinski parameters, confirming their suitability for oral or topical applications. Catechin and Naringenin exhibited high absorption and favorable skin permeability, making them ideal candidates for wound-healing formulations.

Toxicity and Cytotoxicity

Toxicity results demonstrated that Catechin and Naringenin are safe and non-cytotoxic, supporting their potential use in drug formulation. Quercetin, although active, was flagged as cytotoxic and thus less favorable for wound treatment.

Binding Affinity Analysis

Naringenin showed the strongest binding affinity with TGF-β (–9.5 kcal/mol), indicating a possible role in enhancing tissue repair and angiogenesis. Catechin strongly interacted with VEGFR (–8.8 kcal/mol), suggesting its ability to stimulate endothelial growth and vascularization. Kaempferol's affinity toward FGFR1 (–8.6 kcal/mol) further reinforces its contribution to wound-healing mechanisms.

Interaction Profile Evaluation

The presence of multiple hydrogen bonds and aromatic π-π interactions among the top-ranked complexes confirms the stability of ligand–receptor interactions. These networks contribute to effective inhibition or activation of the targeted pathways, highlighting the multi-target nature of guava flavonoids.

Docking Validation

Low RMSD values (< 2 Å) confirmed that the generated docking poses were reliable. Ligand-efficiency analysis also proved that smaller molecules, such as Naringenin and Catechin, achieved optimal binding per heavy atom—further validating their effectiveness as lead compounds.

Integrative Interpretation

Combining ADME, toxicity, and docking results, Catechin, Naringenin, and Kaempferol emerged as the most promising bioactives. Their strong affinities for angiogenic and antimicrobial targets demonstrate a dual mechanism beneficial for diabetic-wound healing. Among them, Catechin was the most favorable, exhibiting excellent safety, bioavailability, and stability.

Conclusion

The results of this study indicated that the selected guava (*Psidium guajava* L.) phytochemicals (Catechin, Kaempferol, Naringenin, and Gallic Acid), possessed strong pharmacological potential for promoting diabetic wound healing due to their favorable physicochemical, toxicity, and docking characteristics. All compounds complied with Lipinski's Rule of Five, showing high gastrointestinal absorption and non-toxic properties, which support their suitability as drug-like molecules. Among them, Catechin exhibited the most promising results, having the highest LD_{50} value and strongest binding affinity toward VEGFR and PBP, indicating its potential role in enhancing angiogenesis and antimicrobial activity.

While Naringenin demonstrated the strongest binding energy with TGF-β, suggesting effective regulation of growth factors in wound repair, Kaempferol showed a significant interaction with FGFR1, contributing to tissue regeneration. These results suggest that guava-derived compounds can target both angiogenic and antimicrobial pathways, offering a dual mechanism of action beneficial for diabetic wound healing. Furthermore, all top ligands showed stable molecular interactions through hydrogen bonding and hydrophobic contacts, confirming their binding stability and potential bioactivity.

Therefore, the guava phytochemicals—particularly Catechin—have been proven to be viable and sustainable natural alternatives for therapeutic wound-care agents. Their strong binding affinities, favorable ADME profiles, and non-toxic nature make them reliable candidates for future pharmaceutical formulations. Further *in vitro* and *in vivo* studies are recommended to validate these computational findings and to explore

the clinical potential of guava extracts in diabetic wound management.

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Declaration of Conflicting Interests

The authors declare no potential conflicts of interest with respect to the research, authorship and publication of this article.

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