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Unravelling potential molecular targets of quercetin antibacterial activity against *Staphylococcus aureus*-infected wound through gene network, *in silico*, and *in vitro* approaches

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ABSTRACT

Introduction: *Staphylococcus aureus* is a pathogenic bacterium commonly present in chronic wounds and can contribute to clinical complications, particularly among diabetic patients. Quercetin is a natural flavonoid with outstanding antioxidant and antibacterial properties. This study aimed to elucidate the molecular mechanisms of quercetin in modulating *S. aureus*-infected wound healing, particularly by identifying key target genes, *in silico* molecular docking verification, and investigating its *in vitro* antibacterial properties.
Methods: A bioinformatics investigation was conducted to identify interrelated genes, using a Venn diagram and protein–protein interaction (PPI) analysis. Hub genes were identified using the Maximal clique centrality (MCC) and Density of maximum neighbourhood component (DMNC) algorithms. Molecular docking assessed interactions between quercetin and key targets (TP53 and CYP3A4), followed by *in vitro* validation of quercetin's antibacterial activity against *S. aureus*.
Results: Protein-protein interaction (PPI) and Gene Ontology (GO) analyses showed that quercetin regulates the genes involved in apoptosis (*TP53*, *MCL1*), oxidative stress (*CYP3A4*, *CYP2E1*), and the insulin-related pathway (*INS*, *SLC2A2*, *HNF1A*). *TP53*, *INS*, and *CYP3A4* exhibited the highest DMNC and MCC scores. Quercetin bound to CYP3A4 (−6.74 kcal/mol) and TP53 (−5.89 kcal/mol), and stabilized by multiple hydrogen and hydrophobic interactions. *In vitro* antibacterial assays confirmed that quercetin inhibited *S. aureus* growth in a dose-dependent manner with MIC and IC_{50} values of 62.5 and 111.23 µg/mL, respectively.
Conclusion: The integrated gene network and molecular interaction approach highlight quercetin's potential as a bioactive compound for accelerating healing in infected and diabetic wounds.

Implication for health policy/practice/research/medical education:
Quercetin exhibits antibacterial activity against *Staphylococcus aureus*. This study highlights the potential of quercetin as a therapeutic agent for the treatment of *S. aureus*-infected wounds.

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Introduction

Skin injury reduces the skin's ability to protect itself, allowing bacteria normally sequestered on its surface to penetrate the skin (1,2). Acute wounds generally progress through normal stages of healing, with apparent signs of recovery typically observed within four weeks. They restore their structural integrity through multiple molecular pathways that promote cell proliferation. On the other hand, chronic wounds are characterized by non-migratory epidermis, abnormal fibroblast functions, reduced vascularization, persistent inflammation, prolonged infection, tissue necrosis, and failing to heal for more than 4 weeks (1,2). Overall, wound healing is affected by multiple factors, including local wound

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conditions, systemic mediators, the nature of the injury, and the presence of underlying diseases; estimated to affect 1–2% of the global population (3). Bacterial infection is one of the major causes of chronic wounds, which prolongs the inflammatory phase of the healing process. Some types of bacteria that have the potential to cause infection include *Staphylococcus aureus*, *Actinomyces* spp., *Clostridium* spp., *Escherichia coli*, *Proteus* spp., *Neisseria* spp., *Vibrio vulnificus*, and *Candida* spp. (4,5). A previous study presented that the most common bacteria in infected wounds were *Staphylococcus* spp. (44.4%), *E. coli* (13.6%), *Pseudomonas aeruginosa* (12.9%), *Enterococcus faecalis* (10.8%), *Klebsiella pneumoniae* (8.4%), *Proteus* spp. (3.7%), *Enterobacter spp. (3%), Serratia* spp. (1.3%), *Citrobacter* spp. (1.1%), and *Acinetobacter* spp. (0.7%) (6). *S. aureus* is the most prevalent bacterium causing skin infections in chronic wounds, found in more than 34.7% to 38.7% in clinical samples of infected wounds (5,7,8).

S. aureus disturbs simultaneous molecular pathways involved in the wound healing stages, thereby interfering with the wound healing process (9). It activates pro-inflammatory macrophages and neutrophilic cells, which target the host immune system and promote the release of pro-inflammatory cytokines, including tumor necrosis factor (TNF), interleukin (IL), and matrix metalloproteinase (MMP). However, the dysregulated immune environment in chronic wounds induces bacterial proliferation, sustaining a cycle of continued inflammation and biofilm formation (5,10). Consequently, effective antibacterial therapy is essential for the treatment and prevention of wound infections. However, an uncompliant regimen of antibacterial therapy leads to bacterial resistance to these antibacterial agents (11). Therefore, an alternative strategy is urgently needed to treat infected wounds, one of which is by using natural compounds. One of the most promising approaches is the application of natural bioactive compounds, which exhibit potent antibacterial activity and reduce reliance on synthetic antibiotics and the frequency of hospitalization associated with chronic wound infections (12).

Quercetin, a flavonoid polyphenol group, is widely distributed in various natural products. Flavonoid compounds have distinctive biological characteristics that may reduce the risk of infection (13-15). It exhibited multiple pharmacological effects such as antioxidants, anti-SARS-CoV-2, anticancer, antiviral, antimicrobial, anti-inflammatory, cardioprotective, and anti-obesity activities. It has been demonstrated that such pharmacological activity may serve to treat cardiovascular disease, cancer, allergic reactions, inflammation, and arthritis (14,16,17). It also enhances mesenchymal stem cell and keratinocyte migration during wound healing and accelerates *in vivo* cutaneous wound healing by modulating multiple cytokines and growth factors (17-20). Moreover, quercetin revealed antibacterial activity against a lot of bacterial strains, especially those associated with the respiratory, urinary, gastrointestinal, and skin systems. Its antibacterial mechanisms include inhibiting cell walls and membranes synthesis, altering bacterial cell permeability, hindering deoxyribonucleic acid (DNA) synthesis, suppressing enzyme activity, inhibiting virulence factor expression, and preventing biofilm formation (14,21). Specifically, quercetin biofilm-forming impedes *S. aureus* proliferation in chronic wound infection in diabetic mice (4). Most existing studies have investigated quercetin activity in accelerating wound healing and impeding bacterial infection in simplified bacterial culture models, which do not fully represent the complex biological condition of the wound microenvironment (17-20).

S. aureus-infected wounds represent a dynamic microenvironment characterized by bacterial attachment, colonization, inflammation, oxidative stress, and delayed tissue regeneration. These reciprocal interactions between host and bacteria crucially interfere with wound healing stages and may alter the pharmacological response of antibiotic agents. Further, multiple-target antibacterial mechanisms in wound microenvironments have not been explored. To address this gap, this study used bioinformatics analysis to assess genes affected by quercetin in *S. aureus*-infected wounds. To clarify how the molecule interacts with its biological targets, it is crucial to investigate network pharmacology, which combines bioinformatics and network-based analytical tools. Network pharmacology was originally proposed by Hopkin in 2007 to construct a multi-level "disease–target–drug" network to investigate the relationships between medications and illnesses and how pharmaceuticals function (22,23). Network pharmacology combined with molecular docking has been widely applied to explore natural compounds' targets as pure compounds or in plant extracts in wound healing (24-28). Thus, it assists in accelerating the discovery of potential drug targets, improves the evaluation and optimization of drug candidates, and supports the assessment of potential adverse effects and forecasting drug resistance (29,30). Furthermore, molecular docking and simulation approaches were applied to investigate selected protein-ligand interactions to facilitate the discovery of effective antibacterial agents. This study aimed to elucidate the molecular mechanisms of quercetin in modulating *S. aureus*-infected wound healing, particularly by identifying key target genes, *in silico* molecular docking verification, and investigating its *in vitro* antibacterial properties.

Material and Methods

Materials

Quercetin was procured from Sigma Aldrich (Q4951), and the *S. aureus* used in this study was ATCC 25923. For the biological assays, Mueller–Hinton agar (MHA) (HiMedia, M173), Mueller–Hinton broth (MHB) (HiMedia, M391), dimethyl sulfoxide (DMSO) (Merck, 102952), and

phosphate-buffered saline (PBS) (Gibco, 10010023) were used. All well plates, pipettes, and glassware were obtained from Biologix, Pyrex, and SPL Life Sciences.

Data mining and collection

The canonical SMILES structure of quercetin was retrived from with PubChem CID 5280343 (https://pubchem.ncbi.nlm.nih.gov/quercetin) (31) and employed as the primary input for target prediction. Quercetin-based target genes were subsequently retrieved from multiple public databases, including Similarity Ensemble Approach (SEA) (https://sea.bkslab.org/), ChEMBL (https://www.ebi.ac.uk/chembl/), BindingDB (https://www.bindingdb.org/rwd/bind/index.jsp#), and Swiss Target Prediction (http://www.swisstargetprediction.ch/) (32–35). Moreover, disease and compound-associated genes were also identified from GeneCards (https://www.genecards.org/), PubMed (http://www.ncbi.nlm.nih.gov/), and OMIM (http://www.omim.org/) (36,37). All predicted targets were curated to ensure consistency of gene symbols across the databases. Gene targets were visualized using InteractiVenn (https://www.interactivenn.net/) to identify the specific proteins and genes (Figure 1).

Protein-protein interaction (PPI) network and gene ontology analysis

After the common target genes were identified, a PPI network was constructed. PPI network refers to complex interactions between two or more proteins. PPI data were obtained by identifying proteins that interact directly or indirectly using the STRING software (https://string-db.org/). Moreover, gene network analyses were conducted using Cytoscape 3.10.1 (https://cytoscape.org/), a visualization software tool for molecular interaction networks (38). Subsequently, gene ontology enrichment analysis was investigated using ShinyGO v.082 (https://bioinformatics.sdstate.edu/go/) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis (39,40). The pathway database was sorted according to GO Cellular Component (CC), Biological Process (BP), and GO Molecular Function (MF).

Expression level analysis

The DMNC and MCC algorithms from the Cyto-Hubba plugin from Cytoscape 3.10.1 were employed to screen the top 10 genes with the highest correlations in the PPI network (31), recognized as hub genes. The selected hub genes were associated with wound-related processes. The bioinformatics experiment was carried out using a computer provided with an 11th Gen Intel(R) Core (TM) i5-1155G7 processor operating at 2.50 GHz and 8 GB of RAM.

In silico molecular docking

The molecular structures of TP53 (4MZI) and CYP3A4 (7KSA) were acquired from the RCSB Protein Data Bank (https://www.rcsb.org/), while the ligands were prepared using BIOVIA Discovery Studio 2021. Ligand protonation was carried out using Gasteiger charges, and Kollman charges were assigned to the macromolecular structure using AutoDockTools 1.5.7. Quercetin was sourced from PubChem CID 5280343 (https://pubchem.ncbi.nlm.nih.gov/quercetin). The ligands were placed at coordinates x = 12.566, y = 2.803, z = 5.125 for 4MZI and x = -13.961, y = -21.596, z = -8.264 for 7KSA. A grid box measurement of 70 × 70 × 70 with a spacing of 0.375 Å, and a genetic algorithm with 100 GA runs was employed. The resulting protein-ligand complexes were analyzed in both 2D and 3D using BIOVIA Discovery Studio 2021, providing insights into binding energy and interaction characteristics (41).

Agar diffusion assay

The antibacterial activity of quercetin was observed using the agar diffusion assay on MHA. *S. aureus* suspensions (0.5 McFarland) were inoculated onto the MHA seed layer using the double-layer pour plate method (42). Wells were made using an agar well punch, then 20 µL of quercetin solutions at 30, 50, and 100 mg/mL in 10% DMSO (negative control)

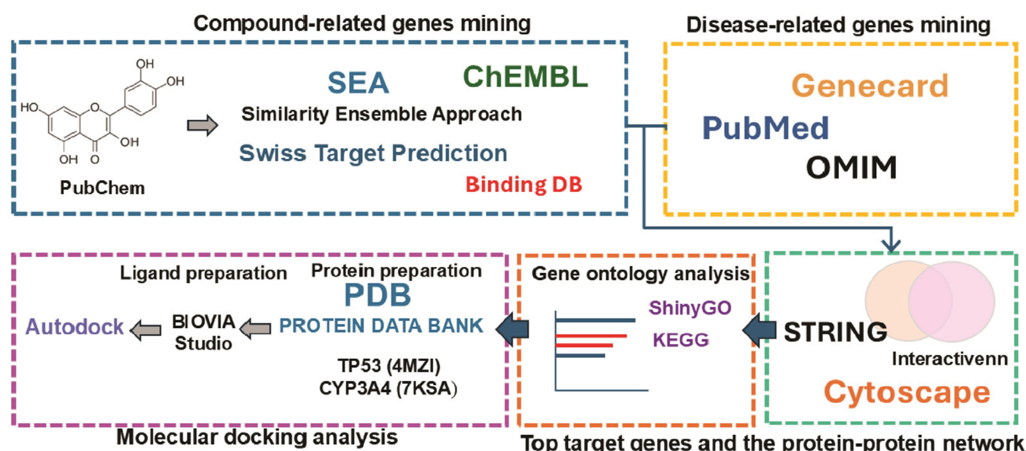


Figure 1. Workflow of the bioinformatics and molecular docking analyses of quercetin against *S. aureus*-infected wounds.

and amoxicillin (positive control) were dispensed into each well. Petri dishes were incubated for 24 hours at 37 °C, and the inhibition zone diameter was measured thereafter.

Determination of minimum inhibitory concentration (MIC)

The MIC was measured by the broth microdilution assay (43) with slight modifications. Briefly, quercetin was dissolved in DMSO and diluted with MHB to obtain concentrations of 1000, 500, 250, 125, and 62.5 µg/mL. Each concentration, as well as 5% DMSO as a negative control, was added in triplicate (100 µL per well) into a 96-well plate. Subsequently, *S. aureus* culture in MHB, equal to 0.5 McFarland standard (approximately 1-2 × 10^8 CFU/mL), was placed in each treatment and control well. The well plate was then incubated for 16 to 24 hours at 37 °C. The bacterial growth was evaluated using an ELISA microplate reader by measuring turbidity at 500 nm. Furthermore, the IC_{50} was defined as the lowest concentration that inhibited 50% of bacterial growth.

Results

Bioinformatic analysis of quercetin's effect on *S. aureus*-infected wounds

Based on data mining and collection results, 10,662 *S. aureus* wound genes and 12,114 wound healing genes were obtained. These genes were compared with 100 genes related to quercetin. The Venn diagram and PPI network analysis revealed the presence of 57 genes associated with *S. aureus* wound and wound healing that were affected by quercetin (Figure 2b). Among 57 genes, there were two proteins outside of the PPI network: Death-associated protein (DAP) and DAP3 (Figure 2c). DAP acted as a positive mediator of interferon-

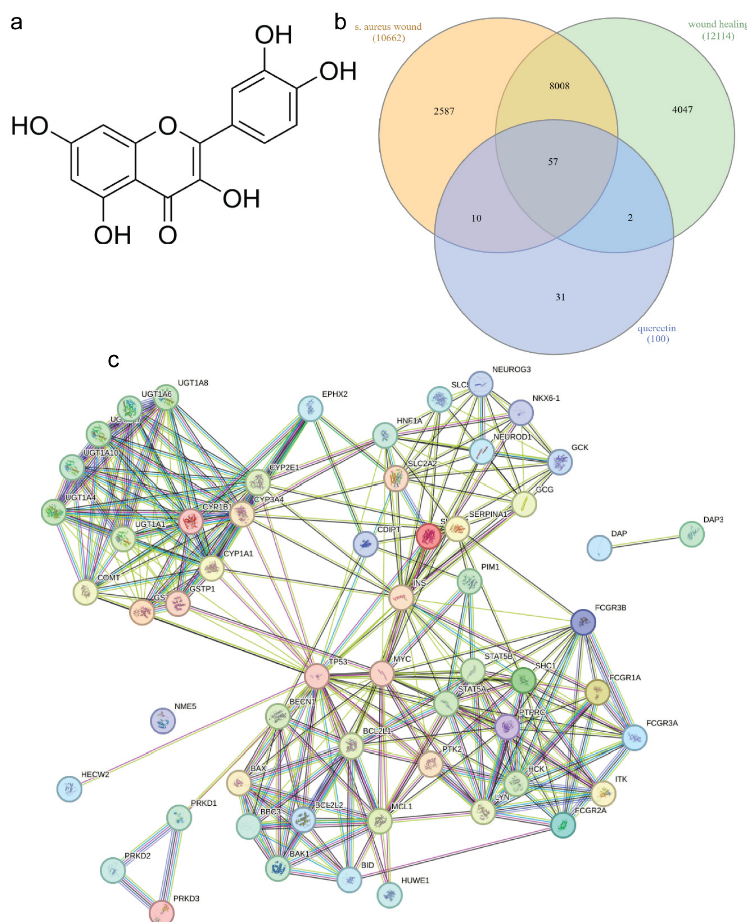


Figure 2. Top quercetin-associated genes and proteins related to *S. aureus*-infected wounds. (a) Quercetin structure, (b) Venn diagram of quercetin and *S. aureus*-infected wounds modulated genes, (c) Protein-protein interaction (PPI) network of the interrelated genes. DAP: Death-associated Protein; DAP3: Death-associated Protein 3; UGT: Uridine diphosphate (UDP)-glucuronosyltransferase; COMT: Catechol-O-methyltransferase; GST: Glutathione S-transferase; TP53: Tumor protein p53; INS: Insulin; MYC: Cellular myelocytomatosis oncogene; CYP3A4: Cytochrome P450 3A4; CYP2E1: Cytochrome P450 2E1; BCL2L1: BCL-2-like protein 1; CYP1A1: Cytochrome P450 1A1; MCL1: Myeloid cell leukemia 1; SHC1: SHC-transforming protein 1; LYN: Tyrosine-protein kinase Lyn; GSTP1: Glutathione S-transferase Pi 1; UGT1A1: UDP-glucuronosyltransferase 1A1; GSTM1: Glutathione S-transferase Mu 1; UGT1A6: UDP-glucuronosyltransferase 1A6; UGT1A10: UDP-glucuronosyltransferase 1A10; SERPINA1: Serpin Family A Member 1 (alpha-1 antitrypsin); EPHX2: Epoxide Hydrolase 2; NEUROG3: Neurogenin 3; NEUROD (NEUROD1): Neuronal Differentiation 1; HNE1A: Hepatocyte Nuclear Factor 1 Alpha; GCG: Glucagon; PIM1: Proto-Oncogene, Serine/Threonine Kinase; NKX6-1: NK6 Homeobox 1; CDIPT: CDP-Diacylglycerol–Inositol 3-phosphatidyltransferase; UGT1A7: UDP-glucuronosyltransferase 1A7; and UGT1A4: UDP-glucuronosyltransferase 1A4.

gamma-induced programmed cell death, while DAP3, a GTP-binding protein of the ribosomal small subunit, participated in the interferon-induced apoptotic process (44-46). The enclosed PPI network includes oxidase-reductase enzymes, apoptosis and proliferation-related proteins, diabetes-related proteins, and transcription factors (Figure 2c).

The interrelated genes were further analyzed using Gene Ontology to investigate their roles in the infected wound. In the cellular component (CC) category, the interfered genes were predominantly associated with the BCL-2 family protein complex, indicating that the potential role of quercetin in modulating wound healing, since BCL-2 is a proto-oncogene that suppresses apoptosis, the process of programmed cell death (47,48) (Figure 3). Quercetin-associated genes were mostly involved in enzymatic and binding activities related to redox balance, metabolism, and immunological regulation, according to GO enrichment analysis of the MF category. BH3 domain binding, fatty acid omega-1 hydroxylase activity, vitamin D 24-hydroxylase activity, oxidoreductase activity working on paired donors involving incorporation or reduction of molecular oxygen, along with IgG receptor activity, were among the most enriched terms (Figure 4). The enriched terms in the biological process category were mostly linked to apoptosis, metabolism, and the control of oxidative stress (Figure 5). Flavonoid metabolic process, toxin metabolic process, cellular glucuronidation, xenobiotic metabolic process, and fatty acid metabolic process were the most highly enriched pathways, suggesting that quercetin may regulate redox homeostasis and detoxification in infected wound tissue.

Furthermore, the MCC and DMNC algorithms measure gene connectivity based on interaction levels, with each

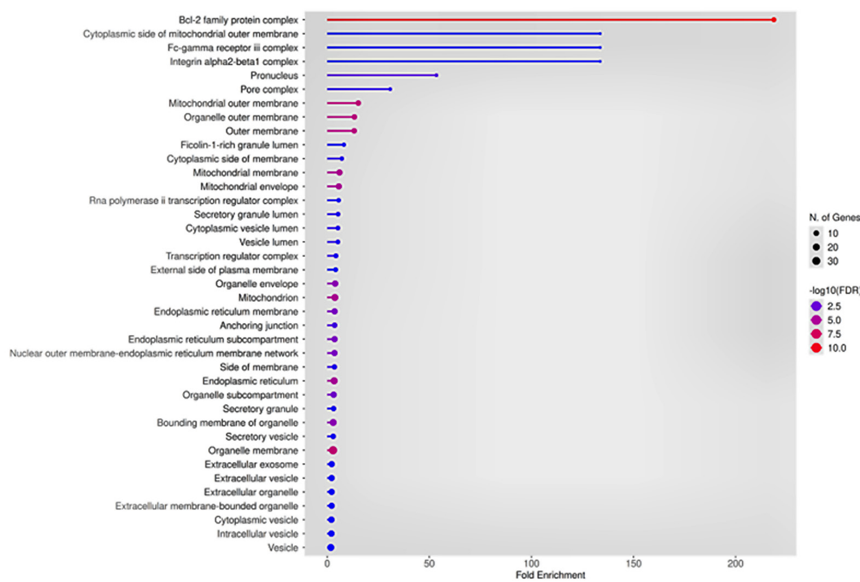


Figure 3. Gene ontology analysis of quercetin in cellular components.

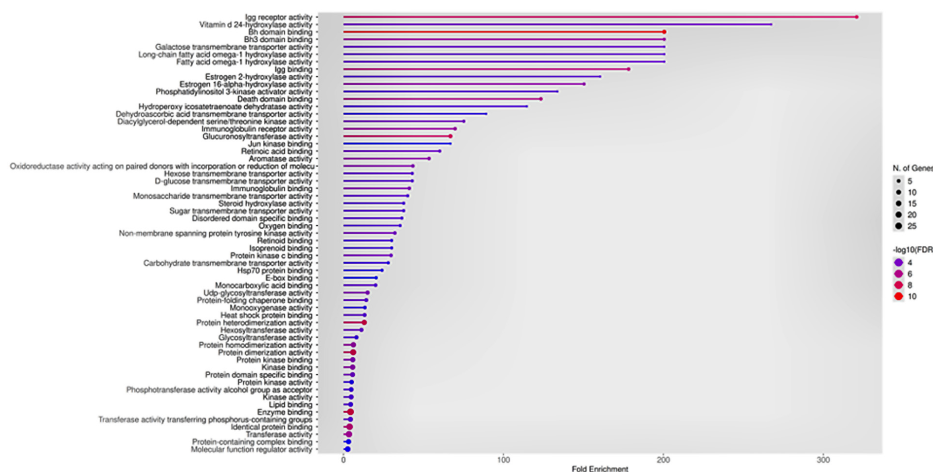


Figure 4. Gene ontology analysis of quercetin in molecular function.

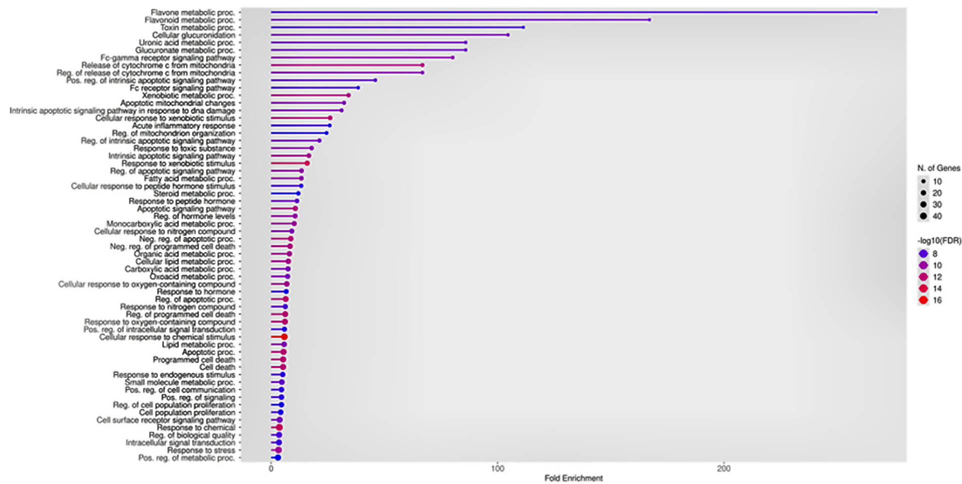
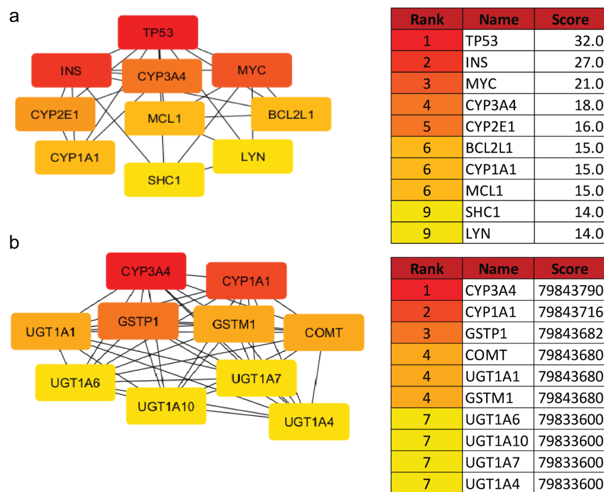


Figure 5. Gene ontology analysis of quercetin in biological process.

algorithm identifying the top-ranked genes among the 10 highest-scoring results of each analysis. The ranks and their scores, presented in Figure 6, represent the genes most strongly affected by quercetin in *S. aureus* wound and wound healing. Based on the DMNC algorithm, *TP53* was identified as the highest-scoring gene targeted by quercetin (Figure 6a). Meanwhile, based on the MCC algorithm, *CYP3A4* was identified as the highest-scoring gene (Figure 6b).



Rank	Name	Score
1	TP53	32.0
2	INS	27.0
3	MYC	21.0
4	CYP3A4	18.0
5	CYP2E1	16.0
6	BCL2L1	15.0
6	CYP1A1	15.0
6	MCL1	15.0
9	SHC1	14.0
9	LYN	14.0

Rank	Name	Score
1	CYP3A4	79843790
2	CYP1A1	79843716
3	GSTP1	79843682
4	COMT	79843680
4	UGT1A1	79843680
4	GSTM1	79843680
7	UGT1A6	79833600
7	UGT1A10	79833600
7	UGT1A7	79833600
7	UGT1A4	79833600

Figure 6. Networking analysis of the 10 highest score quercetin-affected genes involved in *S. aureus*-infected wound (left), as determined by the DMNC (a), and MCC (b), and its ranking algorithms (right). The top 10 genes were: *CYP450 2E1*: Cytochrome P450 2E1; *BCL2L1*: BCL-2-like protein 1; *CYP1A1*: Cytochrome P450 1A1; *MCL1*: Myeloid cell leukemia 1; *SHC1*: SHC-transforming protein 1; *LYN*: Tyrosine-protein kinase Lyn; *GSTP1*: Glutathione S-transferase Pi 1; *COMT*: Catechol-O-methyltransferase; *UGT1A1*: UDP-glucuronosyltransferase 1A1; *GSTM1*: Glutathione S-transferase Mu 1; *UGT1A6*: UDP-glucuronosyltransferase 1A6; *UGT1A10*: UDP-glucuronosyltransferase 1A10; *UGT1A7*: UDP-glucuronosyltransferase 1A7; and *UGT1A4*: UDP-glucuronosyltransferase 1A4.

In silico molecular docking

Molecular docking was applied as a predictive tool for binding potential assessment, so that further studies could investigate the relationship between genes associated with *S. aureus*-infected wounds and quercetin. We selected TP53 and CYP3A4 as target proteins for molecular docking with quercetin. Our molecular docking simulations showed that the interaction between CYP3A4 and quercetin had the highest affinity, followed by the interaction between TP53 and quercetin (Figure 7).

Based on molecular docking analysis, there were three hydrogen bonds formed between TP53 and quercetin, namely Arg181, Met243, and Cys242. There were also three hydrophobic bonds formed, which were His178, Cys176, and Pro177. There were also Van der Waals predictive interactions formed between quercetin and TP53, such as Gly244, Arg248, Ser241, Asn239, and His179. After investigating based on minimum binding energy, the interaction between quercetin and TP53 had a minimum binding energy of -5.89 kcal/mol, respectively (Table 1).

Other than TP53, the interaction between quercetin and CYP3A4 was also predicted using molecular docking. According to the docking results, there were three hydrogen bonds between quercetin and CYP3A4, namely Ala305, Thr309, and Pro434. There were also hydrophobic bonds formed, which included Cys442, Ala448, and Ile369. Furthermore, Van der Waals interactions were also formed, including Ile443, Gly444, Phe435, Ala370, Pro368, Leu364, Val313, Thr310, Asn451, Gly306, Phe447, Phe137, and Phe302. After analyzing based on minimum binding energy, the interaction between quercetin and CYP3A4 had a minimum binding energy of -6.74 kcal/mol (Table 1).

In vitro antibacterial assay

To confirm the bioinformatics and *in silico* prediction, an

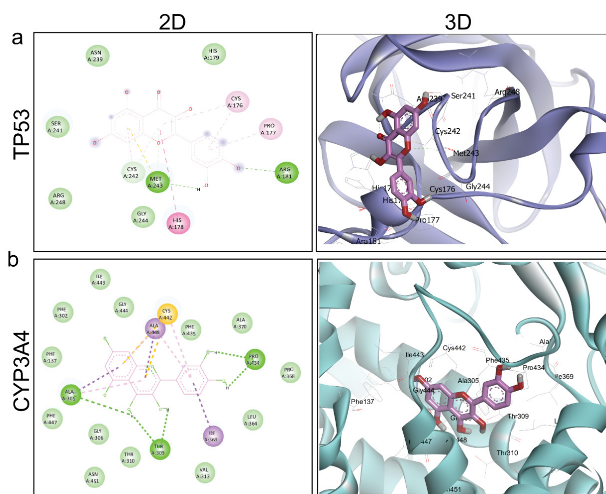


Figure 7. The binding poses of quercetin in the TP53 (a) and CYP3A4 (b) binding pocket in 2D (left) and 3D view (right). Pink, red, and white indicate carbon, oxygen, and hydrogen atoms. Yellow, blue, and green indicate a hydrophobic bond, a hydrogen bond, and a Van der Waals interaction. TP53: Tumor protein p53; CYP3A4: Cytochrome P450 3A4.

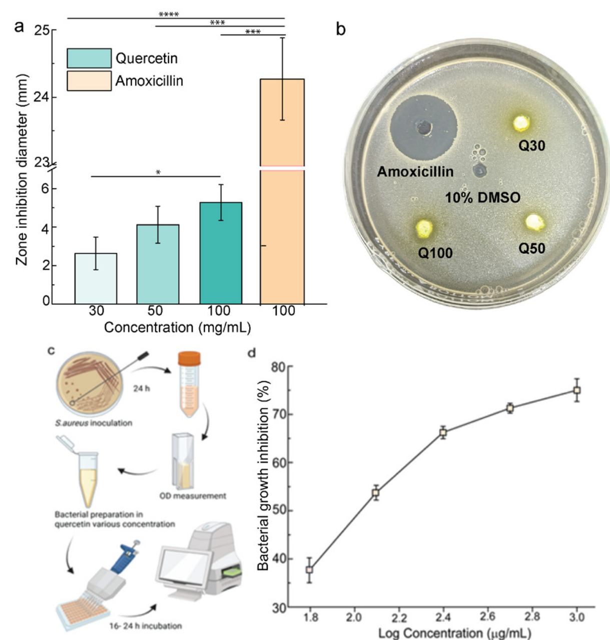


Figure 8. Antibacterial activity of quercetin against *S. aureus*. (a) Quantitative zone inhibition diameter of quercetin (n=3); (b) Image of quercetin antibacterial test; (c) Scheme of broth microdilution assay to determine Inhibitory Concentration 50% (IC_{50}); (d) Determination of quercetin's Minimum Inhibitory Concentration (MIC) on *Staphylococcus aureus* (n=5). Data are expressed as mean ± standard deviation. Statistical significance was calculated using a one-way ANOVA followed by the Tukey Test; **P* ≤ 0.05, *** *P* ≤ 0.001; and *****P* ≤ 0.0001.

antibacterial assay was performed using the agar diffusion assay, then continued microdilution assay to determine the MIC of quercetin on *S. aureus*. The antibacterial activity was evaluated by measuring the diameter of the inhibition zone, which was 2.63 ± 0.85 mm, 4.12 ± 0.96 mm, and 5.28 ± 0.94 mm at the quercetin concentrations of 30, 50, and 100 mg/mL, respectively. Amoxicillin at a concentration of 25 mg/mL was used as a positive control, revealing an inhibition zone diameter of 24.29 ± 0.61 mm (Figure 8a, 8b), whereas the negative control (10% DMSO) exhibited no zone of inhibition. The 100 mg/mL extract showed significantly larger inhibition zones compared to 50 mg/mL and 30 mg/mL ($P < 0.05$). However, the antibacterial activity remained lower than the positive control ($P < 0.001$). Although the inhibition result for quercetin was still lower than amoxicillin, quercetin showed antibacterial activity on *S. aureus*. Moreover, the minimum inhibition concentration was determined with a broth microdilution assay by measuring the turbidity of *S. aureus* culture (Figure 8c). The quantitative analysis of bacterial growth inhibition using the microdilution assay generated a linear regression with the equation of y=30.669x−12.755 and a coefficient of determination (R^2) of 0.918 (Figure 8d). It indicated a strong correlation between concentration and inhibitory effect, with an IC_{50} value of 111.23 µg/mL. Thus, the MIC of quercetin against *S. aureus* was 62.5 µg/mL, defined as the lowest concentration that completely visibly inhibited bacterial growth after 24 hours of incubation.

Discussion

This study focused on gene network analysis by applying bioinformatics to screen the target in *S. aureus*-infected wounds. Gene ontology investigation found that quercetin is involved in mitochondrial-mediated apoptosis and immune cell signaling modulation. It was predicted to target mitochondrial and membrane levels to regulate apoptosis and inflammation, which is a crucial molecular pathway for tissue repair and bacterial clearance in infected wounds. *BCL-2*, an apoptosis-related intracellular marker (47), is the most affected gene in the biological process of gene ontology analysis.

Bacterial infection in chronic wounds is commonly related to diabetes mellitus, identified by impaired insulin (*INS*) production or signalling, causing hyperglycemia and delayed tissue repair. Insulin is a critical regulator of

Table 1. Molecular docking result of quercetin to TP53 and CYP3A4

Protein target	Binding energy (kcal/mol)	H-bond residues	Hydrophobic residues	Van der Waals residues
TP53	-5.89	Arg181, Met243, Cys242	His178, Cys176, Pro177	Gly244, Arg248, Ser,241, Asn239, His179
CYP3A4	-6.74	Ala305, Thr309, Pro43	Cys442, Ala448, Ile369	Ile443, Gly444, Phe435, Ala370, Pro368, Leu364, Val313, Thr310, Asn451, Gly306, Phe447, Phe137, Phe302

glucose metabolism and cellular energy homeostasis, both of which are essential for the proliferation and migration of keratinocytes and fibroblasts during wound healing. Impaired insulin signaling or insulin resistance disrupts these processes, leading to prolonged inflammation and inadequate granulation tissue formation. *SLC2A2* encodes a member of the NeuroD family of basic helix-loop-helix (bHLH) transcription factors involved in the regulation of insulin expression, and its mutations are associated with type II diabetes mellitus (49). Thus, *HNF1A* is broadly expressed in pancreatic β cells, in which a mutation leads to hyperglycemia (50). Moreover, the PPI network displayed Fc gamma receptors (FCGR), IL-2-inducible T-cell kinase (ITK), and Signal transducer and activator of transcription 5 (STAT5). Those proteins are closely related to inflammation in the wound healing process, particularly in an infected wound (51-53). Moreover, *SLC2A2* and *HNF1A* have been linked to type II diabetes mellitus. Those gene mutations lead to hyperglycemia and impaired glucose metabolism and exacerbate the wound microenvironment by accelerating oxidative stress, inflammation, and microbial persistence (49,50), thereby delaying wound closure in diabetic patients. Thus, *SHC1* participates in the downstream signaling cascade of cell-surface receptors, particularly the insulin signalling pathway (54).

The healing process in *S. aureus*-infected wounds may also be affected by the cellular redox process. Reactive oxygen species (ROS) are second messengers for several immunocytes and non-lymphoid cells involved in wound-healing phases. A certain level of ROS production is required to support cell survival signaling and facilitate bacterial clearance (55). Quercetin is predicted to target *LYN*, a tyrosine kinase that serves as a crucial redox sensor, to mediate early neutrophil recruitment to wounds during the healing process (55). In this study, quercetin might have targeted CYPs, including CYP3A4, CYP2E1, and CYP1A1, which are located in the epidermis of our skin (56-60). It may confirm the gene ontology analysis that affects lipid metabolism by converting arachidonic acid (AA) to EET and 12(S)-HETE, thereby activating the AP-1 transcription factor to induce the expression of IL-1β, TNF-α, and IL-6 from an activated macrophage (56,61,62). IL-1β induces angiogenesis and helps the remodeling stage of wound healing (63), while TNF-α attracts fibroblasts and keratinocytes to the wound site and deposits extracellular matrix for granulation tissue formation (64). Moreover, IL-6 influences re-epithelialization and granulation tissue formation processes that are crucial in the healing process (63). However, DAP and DAP3 visualized as isolated nodes disconnected from the main PPI network are likely attributable to stringent confidence score thresholds, the incompleteness of current protein interaction databases, or the context-specific nature of these interactions, rather than to the absence of biological relevance (38,65).

Based on our network pharmacology and molecular docking perspective, *TP53*, *INS*, and *CYP3A4* are suggested as the primary hub genes associated with quercetin in *S. aureus*-infected wound healing. Collectively, these findings demonstrate the predicted targets of quercetin to modulate oxidative stress, inflammation, and apoptosis, thereby facilitating wound healing under infectious conditions. Nevertheless, quercetin has significant drawbacks, notably poor water solubility and low oral bioavailability, which might hinder its clinical application despite its favorable pharmacological properties (66,67). Quercetin has low solubility and bioavailability due to extensive metabolism in the human body (66). Future formulation strategies like nanoparticle encapsulation, liposomal delivery, or co-solvent systems should be taken into consideration to improve quercetin's solubility and bioavailability for wound-healing applications, as these physicochemical limitations may lower the effective concentration of quercetin reaching the target tissue (26,68).

It is crucial to note that network pharmacology, gene ontology enrichment, and molecular docking analysis are computational in nature and should be interpreted as hypothesis-generating tools. Therefore, future studies incorporating gene and protein expression validation and regulation through qPCR and Western blot analysis of predicted genes are crucial to further confirm the regulatory mechanisms predicted in this integrative framework.

Conclusion

This study provides an integrative predictive insight into the molecular mechanism underlying quercetin's antibacterial activity during the healing of *S. aureus*-infected wounds. Based on our network pharmacology and molecular docking perspective, *TP53*, *INS*, and *CYP3A4* are suggested as the primary hub genes associated with quercetin in *S. aureus*-infected wound healing. These genes might regulate apoptosis signaling via tumor suppressor family proteins, maintain metabolic balance through insulin-associated genes, and control redox homeostasis mediated by cytochrome P450 enzymes. Molecular docking analyses predicted to have strong binding affinities between quercetin and CYP3A4 as well as TP53, supporting its dual role in modulating apoptosis and oxidative stress. Furthermore, based on an experimental perspective, *in vitro* antibacterial assays validated quercetin's inhibitory effect against *S. aureus*, demonstrating its therapeutic potential. Overall, this study proposes a mechanistic framework of quercetin as a promising candidate for the management of infected chronic wounds, particularly in diabetic conditions. Thus, future studies of hub gene and protein expression, as well as *in vivo* studies remain to be validated.

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The authors used Claude solely for grammatical

refinement of the manuscript. No AI tools were used for data collection, analysis, or interpretation of the results. All scientific content and conclusions are the authors' responsibility.

Authors' contribution

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Conflict of interests

The authors declare no conflict of interest.

Ethical considerations

This study was performed by following the protocols approved by the Ethics Committee of the Faculty of Health Science, Respati University of Yogyakarta, Indonesia (Approval No.121/FIKES/PL/III/2024).

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