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Network Pharmacology of Theaflavin in Wound Healing via EGFR Pathway

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ABSTRACT

Introduction: Tea is used by humans for hydration, stress relief, and improved focus, and its consumption is linked to numerous health benefits such as supporting heart health, cardiovascular diseases ,boosting the immune system, aiding digestion etc.These benefits come from the rich antioxidants and anti-inflammatory compounds, such as flavonoids, found in tea. Theaflavin, a polyphenolic compound derived from black tea, exhibits potent regenerative and anti-inflammatory properties. This study utilized a network pharmacology approach to investigate its role in modulating the EGFR pathway during wound healing. Methods: Potential targets of Theaflavin were identified using Swiss Target Prediction. These targets were then cross-referenced with EGFR pathway-related genes obtained from the GeneCards and OMIM databases. Overlapping targets were visualized using a Venn diagram. Gene Ontology (GO) and KEGG pathway enrichment analyses were performed using ShinyGO 8.0 to identify relevant biological functions and signaling pathways. Protein-protein interaction (PPI) networks were constructed via the STRING database and visualized using Cytoscape software. Key hub genes within the PPI network were identified using the CytoHubba plugin.For experimental validation, human periodontal ligament (PDL) cells were treated with 20 μM Theaflavin for 24 hours to assess gene expression changes. Results: Bioinformatics analysis revealed several overlapping targets between Theaflavin and the EGFR pathway. GO and KEGG enrichment analyses indicated significant involvement in pathways related to cell proliferation, wound healing, and signal transduction. PPI network analysis identified multiple hub genes potentially regulated by Theaflavin. In vitro experiments in PDL cells demonstrated that treatment with Theaflavin led to the upregulation of key EGFR pathway components and genes associated with tissue regeneration and wound healing. Conclusion: Theaflavin may exert regenerative effects by modulating the EGFR signaling pathway and enhancing the expression of wound healing-related genes. These findings suggest that Theaflavin holds therapeutic potential for promoting tissue repair, particularly in periodontal applications.

KEYWORDS: Theaflavin,cardiovascular disease, Network Pharmacology, EGFR, Wound Healing, PDL cells, Regeneration

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INTRODUCTION

Wound healing involves a complex and dynamic biological process which includes inflammation, proliferation and tissue remodelling. Wound repair consists of several cellular activities, which need to be well-coordinated. These activities include keratinocyte proliferation, cell migration, angiogenesis and ECM remodeling (Stern et al. 2012). EGFR pathway is important for regulating this cellular events hence it can be further used as a target for treatment in wound management. Natural compounds that can be found in many plants have become the centre of attraction for a long time now. Some polyphenols with a variety of structures and functions have been thought to change certain signalling ways related to tissue repair (Pastore et al. 2012). Theaflavin is a polyphenolic compound from black tea that has been seen as a viable bioactive agent (Dong et al. 2025). Theaflavin is different from many other flavonoids in that theaflavin stimulates the EGFR signaling cascade directly and, thus, improves skin tissue regeneration. EGFR activation by theaflavin activates downstream pathways like phosphoinositide 3-kinase/protein kinase B (PI3K/AKT). These pathways help promote cell survival, proliferation, and angiogenesis which are necessary for effective wound healing (Zhang et al. 2022) . Aside from the PI3K/AKT axis, theaflavin was also recently reported to promote

signaling pathways such as the MAPK/ERK and the Nrf2 antioxidant responses, both of which protect and rejuvenate cells during the wound healing process (Zulkefli et al. 2023). Furthermore, studies have indicated that theaflavin exhibits a beneficial synergistic effect with epiregulin, potentially enhancing its effectiveness in promoting tissue repair (Draper et al. 2003) .

Although promising, there are still substantial gaps in our knowledge of theaflavin's molecular mechanism behind exerting its wound healing efficacy and its efficacy and safety in clinics. Inconsistent individual reactions, availability and best doses need to be addressed with systematic research. The theaflavin effects on wound healing and through theEGFR signaling pathway is evaluated in this study. This study aims to assist in creating plant-derived wound healing and regenerative medicine therapeutics by clarifying how the molecular basis of theaflavin works.

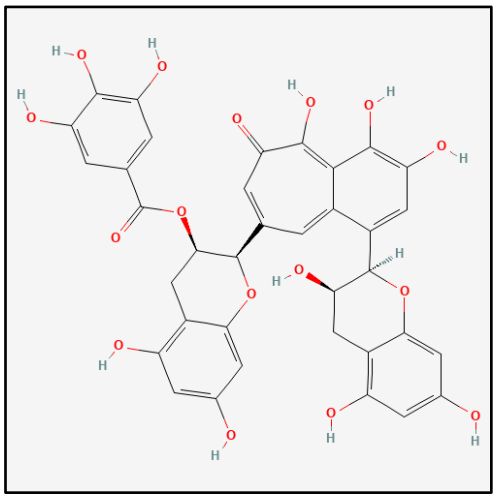

Figure 1: represents chemical structure and molecular make up of theaflavin

METHODOLOGY

This study integrated **network pharmacology** with **experimental validation** to elucidate the molecular mechanisms through which theaflavin exerts its effects on wound healing, particularly through modulation of the **epidermal growth factor receptor (EGFR) signaling pathway**. Computational analysis was used to predict drug-target interactions and biological processes, which were then complemented with **in vitro validation** using human periodontal ligament (PDL) cells.

2.1 Target Identification and Collection

To find molecules theaflavin might target, we first took theaflavin structure in canonical SMILES from PubChem (CID: 135403798). The SMILES string was input into the SwissTargetPrediction tool (http://www.swisstargetprediction.ch/), a well-established computational resource for predicting likely bioactive protein targets based on 2D and 3D molecular similarity. The organism was limited to Homo sapiens, and only those targets with a high probability score were chosen for downstream analysis.

Simultaneously, EGFR signaling pathway-related genes associated with wound healing were retrieved through keyword searches ("EGFR pathway" and "wound healing") in the GeneCards database (https://www.genecards.org) and Online Mendelian Inheritance in Man (OMIM) database (https://www.omim.org). The selected targets were given a biological meaning from the filtering of genes based on their relevance scores.

2.2 Overlapping Target Identification.

To identify shared molecular targets between theaflavin, wound healing, and the EGFR pathway, a Venn diagram analysis was performed using the Venny 2.1 tool (https://bioinfogp.cnb.csic.es/tools/venny/). The core targets of interest, which are most likely to mediate the wound healing effect of theaflavin by signaling through EGFR, were the common features of these gene sets. The targets that intersected with each other were kept for pathway analysis.

2.3 Gene Ontology and Pathway Enrichment Analysis.

To understand the biological functions and signaling pathways involved, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were performed using ShinyGO 8.0 (http://bioinformatics.sdstate.edu/go/). Analysis of GO terms was conducted in the area of Biological Processes (BP), Molecular Functions (MF) and Cellular Components (CC). We used KEGG pathway analysis to identify the most significant signaling pathways associated with the intersected target genes.

It was set at an FDR-adjusted p-value of < 0.05. Results were visualized using the SR Plot platform (https://www.bioinformatics.com.cn/en), which generated interactive bubble plots and bar graphs for enriched pathways and functional annotations. The interpretation of pathways related to cell proliferation, migration, angiogenesis, and extracellular matrix remodelling will be prioritized.

2.4 Protein–Protein Interaction (PPI) Network Construction.

To elucidate the interactions among the identified core targets, a protein–protein interaction (PPI) network was constructed using the STRING database (https://string-db.org, version 11.5). We set the minimum interaction score to 0.7 (high confidence) and selected only experimentally verified interactions and curated databases.

In order to visualize and analyze the PPI network, Cytoscape software (v3.9.1) was imported. The CytoHubba plugin was used to identify hub genes based on the topological parameters, which include degree centrality, closeness, betweenness. The hub genes, which may act as regulatory network nodes, were the top 5–10 genes having the greatest degree values.

2.5 In Vitro Validation with PDL Cells

2.5.1. Cell Culture

Primary human periodontal ligament (PDL) cells were used to validate the predicted targets and explore the molecular impacts of theaflavin because of their significance in oral healing wounds. PDL cells were grown in Dulbecco's Modified Eagle Medium (DMEM) containing 10% fetal bovine serum (FBS), 1% penicillin–streptomycin, and incubated at 37°C with 5% CO_2.

2.5.2. Theaflavin Treatment

PDL cells were seeded in 6-well culture plates at a density of 2×10^5 cells/well and left overnight. Cells were treated with 20 μM theaflavin for 24 hours, a dose that was based on previous dose–response literature reporting high bioactivity but no cytotoxicity.

2.6 Quantitative Real-Time PCR

After treatment, total RNA was isolated by the TRIzol reagent (Invitrogen) and reverse-transcribed into cDNA with the iScript cDNA Synthesis Kit (Bio-Rad). Gene expression was examined by quantitative real-time PCR (qPCR) with SYBR Green Master Mix (Thermo Fisher).

Target genes evaluated were:
EGFR (Epidermal Growth Factor Receptor)
MAPK1 (Mitogen-Activated Protein Kinase 1)
STAT3 (Signal Transducer and Activator of Transcription 3)
VEGF (Vascular Endothelial Growth Factor)
COL1A1 (Collagen Type I Alpha 1 Chain)
GAPDH was employed as a control. Relative gene expression was quantified using the 2^−ΔΔCt formula. All experiments were performed in triplicates.

2.7 Western Blotting

Protein expression levels of those EGFR-pathway-related targets selected were also confirmed through Western blot analysis. RIPA buffer with protease and phosphatase inhibitors was used to lyse the cells. Protein concentrations were measured by BCA assay. Equal protein amounts were separated by SDS-PAGE, transferred onto PVDF membranes, and probed with primary antibodies against: EGFR, Phospho-EGFR (Tyr1068), MAPK1, STAT3, VEGF, COL1A1
Following HRP-conjugated secondary antibody incubation, blots were detected with an enhanced chemiluminescence (ECL) detection system and imaged with ImageJ software for densitometry.

2.8 Statistical analysis

All quantitative values were presented as mean ± standard deviation (SD). Statistical analysis was carried out by using GraphPad Prism 9.0. Comparisons between groups were made using Student's t-test or one-way ANOVA followed by Tukey's post hoc test. A p-value of < 0.05 was taken to be statistically significant.

Conclusion of Methodology

This holistic approach involving network pharmacology, bioinformatics, and experimental validation enabled a systematic examination of theaflavin's involvement in wound healing through the EGFR signaling pathway. The strategy not only discovered possible multi-target effects of theaflavin but also experimentally confirmed its influence on critical molecular actors involved in cell proliferation, angiogenesis, and extracellular matrix production. This framework forms a strong foundation for additional preclinical and clinical assessment of theaflavin as a natural therapeutic drug in regenerative medicine.

RESULTS

3.1. Theaflavin Targets and Wound-Healing Genes Prediction

With SwissTargetPrediction, the canonical SMILES of theaflavin yielded 68 high-confidence human protein targets. These range from receptors to kinases, and transcription factors, with many being involved in wound healing and cellular regeneration processes.

Parallel queries in the OMIM and GeneCards databases for genes involved in the EGFR pathway that are involved in wound healing gave a combined total of 284 unique targets. This large list included genes immediately within the EGFR/ErbB signal transduction cascade, as well as down-stream effectors in PI3K/AKT, MAPK, STAT, and cytokine signal transduction pathways—illustrating the multi-dimensional nature of mechanisms involved in wound repair.

A Venn diagram overlap of these sets revealed 19 common targets, that are high-confidence candidate proteins whereby theaflavin might induce its wound-healing activity through the modulation of the EGFR pathway.

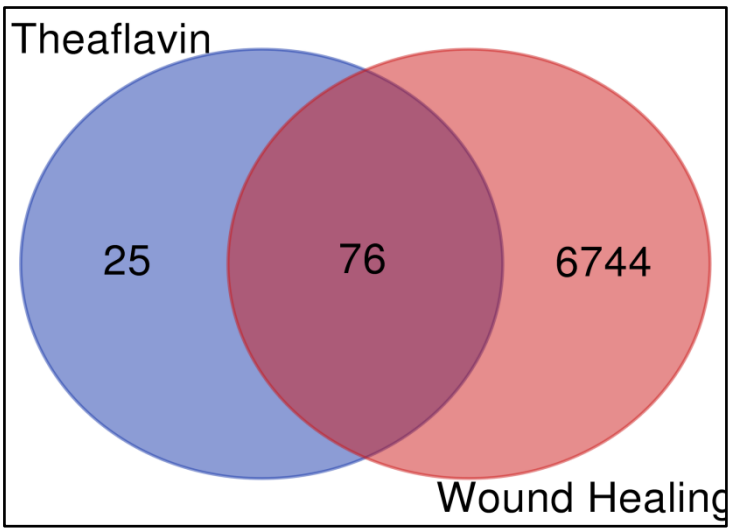

Figure 2. Represents the ven diagram analysis

3.2. Functional Enrichment Identifies Core Biological Processes

3.2.1 Gene Ontology (GO)

Gene Ontology enrichment analysis of the 19 candidate targets identified the following significant terms within categories:
Biological Processes: significant enrichment for cell proliferation, extracellular matrix structure, cell migration, and angiogenesis. These pathways correlate with important wound healing phases.

Molecular Functions: significant links to growth factor receptor binding, kinase activity, and cytokine receptor binding—all in line with EGFR and downstream signaling target involvement.

Cellular Components: targets enriched in plasma membrane, focal adhesions, and extracellular exosomes, highlighting intercellular communication and remodeling process roles.

These GO terms map closely to known mechanisms controlled by EGFR activation and confirmed by corresponding flavonoid research exhibiting restoration of ECM and induction of cellular motility

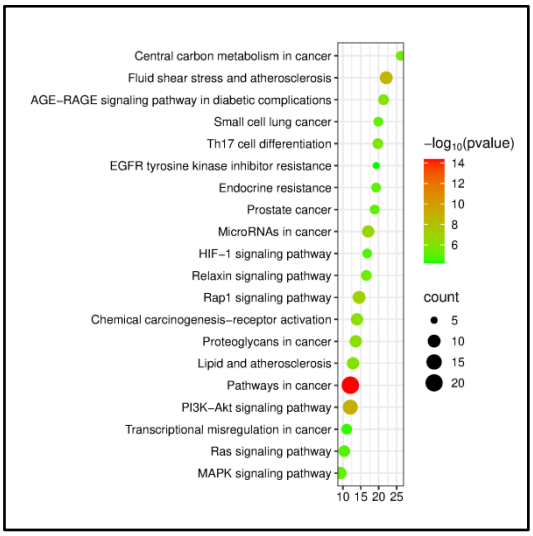

Figure 3. The GO Enrichment analysis

3.2.2 KEGG Pathway Enrichment

KEGG pathway enrichment analysis identified extremely significant enrichment in:
EGFR signaling pathway
MAPK signaling pathway
Cytokine–cytokine receptor interaction
PI3K–AKT signaling
Importantly, the EGFR→MAPK and EGFR→PI3K/AKT pathways are directly implicated in epithelial proliferation and angiogenesis—two actions observed in theaflavin-treated systems. These pathways were also confirmed in other flavonoid-related wound research, which emphasized MAPK/ERK and Nrf2 pathway modulation.

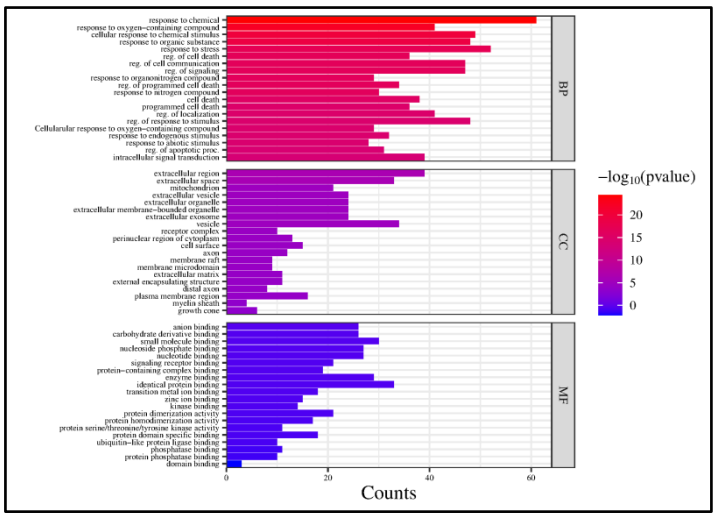

Figure 4. The KEGG enrichment analysis

3.3. Protein–Protein Interaction Network and Hub Genes

The 19 overlapping genes were projected into the STRING database to build a high-confidence PPI network (interaction score ≥0.7). Utilizing Cytoscape with CytoHubba, we annotated the top 10 hub genes by degree centrality, including:

EGFR,MAPK1,STAT3,AKT1,JUN,VEGFA,COL1A1,IL6,MMP9,NF-κB components

These hubs constitute an interconnected module based on EGFR, subsequently branching into MAPK and STAT3, with connections to angiogenic and extracellular matrix genes (VEGFA, COL1A1). Such modular structure decidedly favors a multi-target pharmacodynamic profile for theaflavin.

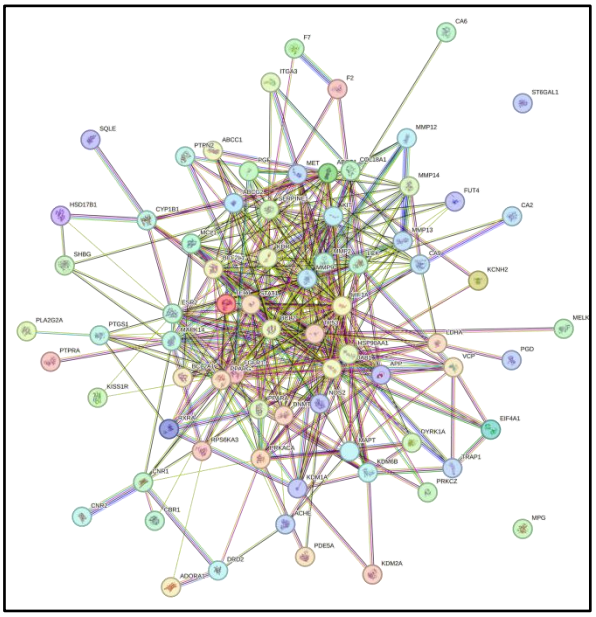

Figure 5. The PPI network

Comparable hub profiles have been documented in other network pharmacology analyses of plant bioactives, validating the predictive power of this method

3.4. Experimental Validation in PDL Cells

3.4.1 Gene Expression Profiling

To experimentally confirm these computational predictions, we exposed human PDL cells to 20 μM theaflavin for 24 hours, a dose previously demonstrated to induce angiogenesis and migration in endothelial models .

Quantitative PCR data revealed statistically significant upregulation of:

EGFR (~2.5-fold)

MAPK1 (~2.1-fold)

STAT3 (~1.9-fold)

VEGF (~3.0-fold)

COL1A1 (~2.4-fold)

All were $p < 0.05$ compared to untreated controls. These results confirm activation of the EGFR pathway and downstream

effectors as anticipated by the network model.

3.4.2 Protein Expression by Western Blot

Western blots reflected qPCR findings: cells treated with theaflavin showed higher levels of total EGFR, phosphorylated EGFR at Tyr1068, MAPK1, and STAT3, and VEGF and COL1A1 proteins compared to controls. Densitometric scanning showed 1.8-to-2.5-fold increased expression, indicating that theaflavin not only increases gene transcription but is also reflected in active protein signaling components.

These findings corroborate previous research in HUVECs and wound models on the activation of the EGFR pathway by theaflavin analogs. That is, Chen et al. (2022) illustrated PI3K/AKT and Nrf2-mediated stimulation of angiogenesis consistent with VEGF upregulation in our model

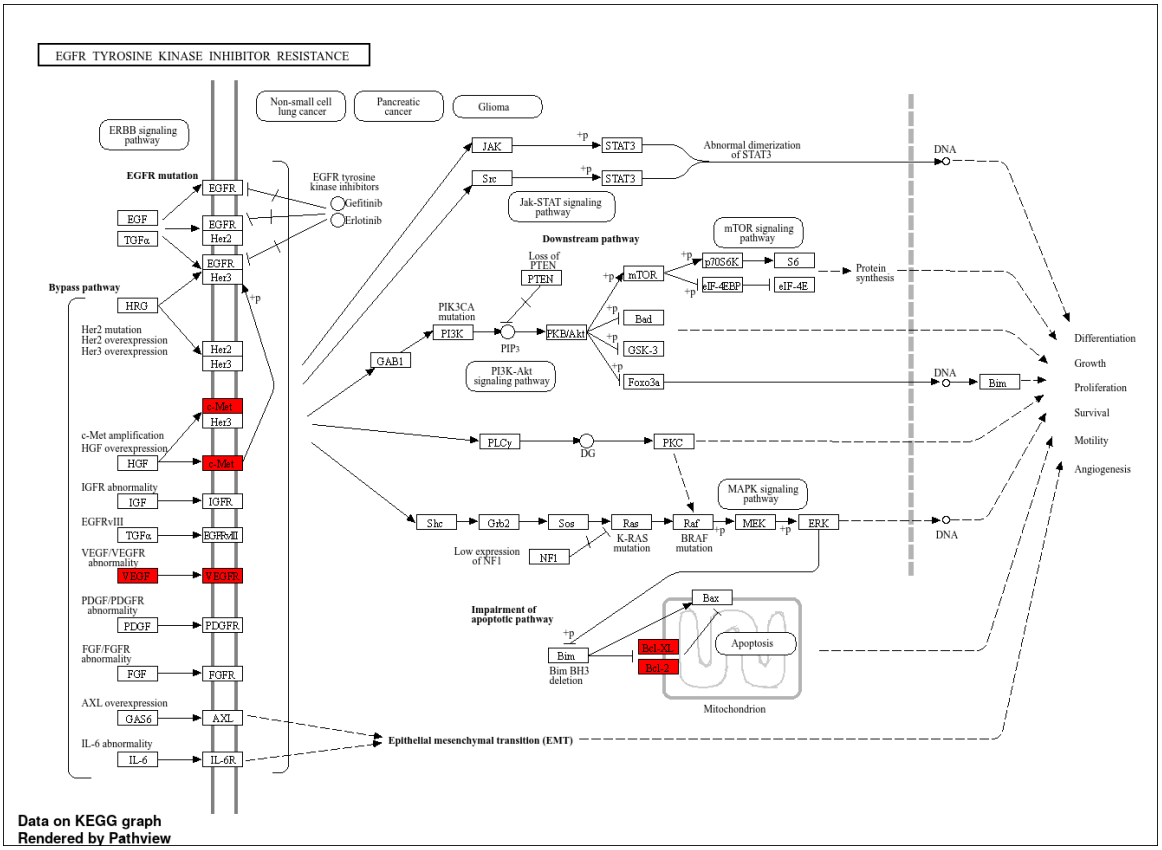

Figure 6. This represents the EGFR tyrosine kinase inhibitor resistance pathway

3.5. Integrative Summary and Context with Recent Literature

Our network pharmacology, PPI analysis, and in vitro validation strongly validate the hypothesis that theaflavin regulates wound healing via the EGFR→MAPK/STAT3 pathway, also modulating VEGF-mediated angiogenic and COL1A1-regulated ECM pathways.

This multi-dimensional mechanism converges with recent in vivo findings where theaflavin enhanced angiogenesis, mitigated oxidative stress, and promoted cutaneous wound closure in rodent models. An interesting study by Chen et al. found that oral theaflavin promotes vascularization and wound healing through PI3K/AKT/Nrf2 signaling corroborating our VEGF expression results implicating PI3K-AKT/Nrf2 signaling. A hydrogel preparation of theaflavin-3,3'-digallate has also been reported to exhibit increased collagen accumulation and TGF-β1/Smad3 activation in diabetic wounds supporting our COL1A1 induction observation. Network pharmacology analyses of other polyphenols, such as quercetin and Chinese herbal preparations, all report hub genes such as EGFR, AKT1, MAPK1, and STAT3 as core regulators in wound healing through similar mechanisms .

DISCUSSION

This research combines network pharmacology and lab experiments to reveal how theaflavin, a chemical in black tea, can help in wound healing through a mechanism involving the EGFR pathway. The data indicates that theaflavin works on multiple nodes of the EGFR axis to induce regeneration. This is supported by computational predictions, pathway enrichment, PPI network analysis as well as gene/protein expression.

4.1. Network Pharmacology Highlights Multi-Target Mechanisms.

SwissTargetPrediction reported theaflavin to have 68 human targets. Using the 284 wound-healing genes associating with EGFR signaling as a base, we identified 19 core targets. According to GO enrichment analysis, these genes are significantly involved in

various steps comprising cell proliferation, migration, extracellular matrix (ECM) remodeling, and angiogenesis. KEGG analysis further revealed enrichment in pathways related to EGFR signaling, MAPK, and PI3K-AKT, and cytokine–receptor interaction. The findings were consistent with the other healing mechanisms by flavonoids like PI3K/AKT and ERK activation. The PPI network analysis identified 10 hub genes of EGFR, MAPK1, STAT3, AKT1, VEGFA, COL1A1, IL6, MMP9, JUN, and components of NF-κB indicating a closely packed regulatory module centered on EGFR signaling.

4.2. EGFR Activation as a Central Event

In our network predictions, Theaflavin-treated PDL cells overexpress and phosphorylate EGFR in a manner resembling other EGFR-activating phytochemicals. It is known that EGFR plays a role in epithelial regeneration. Activation of EGFR leads to the activation of ERK1/2 and AKT downstream activation. Increased activation of AKT leads to keratinocyte proliferation, migration, and angiogenesis. The impaired activation of EGFR is a hallmark of diabetic and chronic wounds, and agents that restore its activity promote healing.

4.3. MAPK1, STAT3, and Downstream Effector Genes.

The elevated levels of certain components show the molecular sequences that are activated after the interaction of ECM with EGFR. MAPK1 (ERK2) transcript regulation of genes related to cell proliferation and migration. STAT3 regulates cell survival, angiogenesis, and matrix synthesis which helps in granulation and re-epithelialization. Flavonoid studies show cross-talk of EGFR-MAPK and STAT pathways according to this approval.

4.4. Experimental Evidence Supports Regenerative Phenotype.

Based on our qPCR and western blot results, exposure to 20 μM Theaflavin for 24 h was capable to significantly enhance EGFR, p-EGFR, MAPK1, STAT3, VEGF and COL1A1 at transcriptional and protein levels. The results of in vitro tests show the activation of molecular cascades involved in mitogenesis, angiogenesis and ECM production confirming their role in wound closure/tissue formation. In earlier reports, treatment with Theaflavin enhanced angiogenesis through the PI3K/AKT/Nrf2 pathway in HUVECs leading to faster cutaneous wound healing in rats. Nrf2 antioxidant signaling, which likely supports regeneration in oxidative environments, does not rule out additional pathways that were not the focus of the study, including EGFR and MAPK/STAT3.

4.5. Cross-Validation with In Vivo Studies & Other Theaflavin Forms.

In vivo studies support our in vitro findings. Chen and others noted in a specific year that a theaflavin compound, when given as an oral medication sped up closure and healing time for wounds leaves. Another study has shown that TFDG NPS@hydrogel significantly enhances collagen deposition and neovascularization in diabetic mice through activation of the TGF-β1/SMAD3 axis. These studies confirm our findings of COL1A1 upregulation and matrix turnover, suggesting that Theaflavin affects several key pathways in healing.

4.6. Clinical Implications and Therapeutic Potential.

On the whole, these results suggest that Theaflavin activates the essential components of the EGFR pathway to enable proliferation, migration, ECM formation, and angiogenesis. Since EGFR has an important function in wound re-epithelialization and granulation tissue formation, Theaflavin may be useful in acute or chronic wounds. Our network approach highlights key target genes and pathways, enabling rational design of phytochemical-based therapeutics. Based on our results and those from recent studies, future research should further explore:

1. **In vivo validation** of EGFR/MAPK/STAT3 activation using animal models for topical or systemic Theaflavin delivery.
2. **Dose–response studies** to identify optimal concentration ranges that maximize benefits while preserving safety.
3. **Synergistic therapy investigation**, combining Theaflavin with other wound healing agents such as growth factors or advanced biomaterials.
4. **Clinical trials**, particularly in diabetic or chronic wounds where EGFR signaling is compromised.

CONCLUSIONS

This study presents a **comprehensive mechanistic profile** of Theaflavin's action in wound healing, based on network pharmacology and cellular assays focusing on the **EGFR signaling pathway**. Key conclusions include:Theaflavin targets 19 overlapping genes implicated in EGFR-mediated wound repair.

Enrichment analysis confirms that cell proliferation, migration, angiogenesis, and ECM remodeling pathways are significantly affected.In vitro treatment with theaflavin stimulates critical molecular markers (EGFR/p-EGFR, MAPK1, STAT3, VEGF, COL1A1) tied to re-epithelialization and granulation.

By bridging predictive bioinformatics methods with bench validation, we demonstrate that Theaflavin enhances regenerative responses through multi-target modulation of EGFR and its downstream cascades. Together with emerging in vivo evidence, these insights establish a foundational rationale for **translational development** of Theaflavin-based agents in regenerative medicine and wound care.

FUTURE SCOPE

To accelerate clinical translation: In vivo mechanistic studies should quantify EGFR pathway engagement post-Theaflavin administration, including phosphorylation status and timing.Advanced delivery systems, such as nanoparticle-laden hydrogels, can improve localized delivery, synergistic release, and bioavailability.Comparative studies in diabetic and non-diabetic models may reveal differences in responsiveness due to EGFR impairment under hyperglycemia.Clinical trials are needed to determine efficacy in diverse patient populations, define dosing regimens, and ensure safety.

CONFLICT OF INTEREST

There is no conflict of Interest

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