Community Acquired Infection

ORIGINAL ARTICLE

Integrative bacterial network analysis and molecular docking of *Vitex negundo* bioactives for targeted acne therapy

Amruta Balekundri[1,2], Eknath D. Ahire[3,4,*]

[1]Food and Micronutrient analysis Lab JNMC Campus, KLE Academy of Higher Education and Research, Belagavi 590010, Karnataka, India
[2]KLE College of Pharmacy, KLE Academy of Higher Education and Research, Belagavi 590010, Karnataka, India
[3]Department of Pharmaceutics, MET's Institute of Pharmacy, Savitribai Phule Pune University, Nashik 422003, Maharashtra, India
[4]Department of Quality Assurance, MET's Institute of Pharmacy, Savitribai Phule Pune University, Nashik 422003, Maharashtra, India

ABSTRACT

Background: Acne vulgaris is a common inflammatory skin condition caused by bacterial infections. Herbal remedies have gained attention for their potential in treating acne. This study investigated the antibacterial potential of *Vitex negundo*. Network pharmacology and molecular docking techniques were used to identify key targets and interactions relevant to acne therapy. **Methods:** Targets related to acne vulgaris were identified through open databases and literature reviews. Protein–protein interaction data were obtained from the Metascape and STRING databases, and network construction was performed using Cytoscape. Molecular docking was conducted using AutoDock to assess the binding affinity between *Vitex negundo* bioactives and bacterial targets associated with acne. **Results:** The network analysis revealed several key targets with high degrees of interaction. Molecular docking showed strong binding affinities between selected bioactives and bacterial targets, indicating their potential role in inhibiting acne-related bacterial growth. **Conclusion:** *Vitex negundo* bioactives demonstrate significant antibacterial potential, making them promising candidates for targeted acne therapy.

Key words: acne vulgaris, *Vitex negundo*, network pharmacology, molecular docking, bacterial targets, AutoDock, acne therapy, integrative analysis

INTRODUCTION

Herbal medicines are extensively used worldwide, with nearly 80% of the global population relying on traditional remedies. Despite their effectiveness, these systems often lack proper documentation. Integrating modern tools such as network pharmacology can bridge this gap, providing a scientific framework that can be used to validate and enhance traditional knowledge, paving the way for innovative and evidence-based therapeutic applications.[1,2]

Vitex negundo Linn., commonly known as "nirgundi" in Sanskrit, is a medicinal shrub belonging to the Verbenaceae family, with widespread distribution in tropical and temperate regions, particularly South Asia. Recognized in traditional medicine for its therapeutic potential, this plant is used to treat ailments such as asthma, jaundice, migraines, and wounds.[3] Its bioactive compounds, including polyphenols, terpenoids, and

***Corresponding Author:**
Eknath D. Ahire, Department of Pharmaceutics and Department of Quality Assurance, Savitribai Phule Pune University, Nashik 422003, Maharashtra, India. E-mail: eknathahire05@gmail.com; https://orcid.org/0000-0001-6542-884X
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alkaloids, exhibit antioxidant, antimicrobial, anti-inflammatory, and anthelmintic properties. With its rich phytochemical profile, including p-hydroxybenzoic acid and β-sitosterol, *Vitex negundo* is a promising candidate for pharmaceutical applications, offering an affordable and accessible alternative in primary healthcare systems.[4–6]

Cutibacterium acnes is a key pathogen in acne, and its treatment typically involves oral antibiotics and topical formulations. However, the growing issue of antibiotic resistance poses significant challenges to conventional treatment strategies. Herbal medicines and their advanced formulations constitute viable alternatives, minimizing side effects while providing therapeutic efficacy.[7–9] Leveraging network pharmacology, a cutting-edge tool for elucidating drug mechanisms and multitarget interactions, this study explores the bioactive compounds of *Vitex negundo* and their molecular targets. Utilizing network pharmacology and molecular docking, the study seeks to predict and validate the therapeutic potential of *Vitex negundo* in combating acne.[10–13]

Acne vulgaris is a widespread dermatological condition for which few satisfactory treatments are available. Although conventional therapies such as benzoyl peroxide effectively suppress *C. acnes*, alternative approaches are increasingly being explored due to concerns about irritation and resistance. Among emerging diagnostic techniques, digital fluorescence photography (FP) has been identified as a fast, non-invasive tool for assessing acne and other skin conditions.[14,15] FP utilizes the autofluorescence properties of the skin, which can be excited by UV light and detected using specialized imaging systems. It is particularly useful in cosmetic and skin care research for evaluating pathological skin states such as acne and psoriasis. Recent advancements in FP technology, especially the integration of AI, have enhanced its potential for automated analysis and more precise diagnostics.[16,17] Additionally, new therapeutic approaches, such as *Trachyspermum ammi* (ajwain) essential oil, have shown promise in acne treatment, demonstrating significant reductions in lesion counts, sebum levels, and skin erythema. Given the rapid evolution of FP technology and AI-driven analysis, further research is needed to expand its applications in dermatology and skin care. This article explores the latest developments in acne diagnostics and treatment, emphasizing innovative imaging techniques and emerging natural therapies.[18–20]

Studies have explored the therapeutic potential of *Vitex negundo* in addressing various ailments, including asthma, jaundice, migraines, and wounds. Its bioactive compounds, such as polyphenols, terpenoids, and alkaloids, demonstrate potent antioxidant, antimicrobial, and anti-inflammatory properties. While network pharmacology and docking studies have been conducted on *Vitex negundo*, no literature exists on its bacterial network pharmacology.[21–23] This study investigates its bacterial network pharmacology and molecular interactions with acne-causing bacteria.

MATERIALS AND METHODS

Data mining and target identification

The bioactive compounds of *Vitex negundo* were mined from reliable phytochemical databases, including Dr. Duke's Phytochemical Database (https://phytochem.nal.usda.gov/phytochem/search) and the IMPPAT database (https://cb.imsc.res.in/imppat/), complemented by relevant literature reviews. The molecular targets of *Vitex negundo* phytochemicals were identified using the SwissTargetPrediction database (http://www.swisstargetprediction.ch/). Additionally, disease-specific targets for acne were retrieved from the GeneCards database (https://www.genecards.org/) and the Therapeutic Target Database (TTD; http://db.idrblab.net/ttd/). Common targets between the plant bioactives and acne-associated genes were identified using Venny 2.1 (https://bioinfogp.cnb.csic.es/tools/venny/).[24–26]

Network construction

A drug-disease-target interaction network was constructed using Cytoscape (v3.9.1, https://cytoscape.org/). Unique shapes and colors were employed to visually distinguish the drug, disease, and target node.[27,28]

Drug profile analysis

The drug-likeness properties of the phytochemicals were evaluated using Molsoft (https://molsoft.com/mprop/) based on Lipinski's rule of five. The ADMET profiles of the compounds were predicted using ADMETlab 3.0 (https://admetlab3.scbdd.com/server/screening).[29,30]

Gene ontology (GO) and pathway enrichment analysis

GO and pathway enrichment analyses for the identified targets were performed using Metascape (v3.5.20230501, https://metascape.org/gp/index.html#/main/step1) to determine the molecular mechanisms underlying the therapeutic effects of *Vitex negundo*.[31,32]

Protein–protein interaction (PPI) analysis

PPIs among the identified targets were analyzed using the STRING database (https://string-db.org/), providing insights into functional interactions and biological pathways.[33,34]

Molecular docking

The top five targets with the highest degree of

connectivity from the constructed network were selected for molecular docking studies. Ligand structures of *Vitex negundo* bioactives were retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/), and protein target structures were obtained from the RCSB Protein Data Bank (https://www.rcsb.org/). Discovery Studio Visualizer 2021 was utilized for structure extraction and visualization, while PyRx (https://pyrx.sourceforge.io/) facilitated multiple ligand docking.[23,35,36]

RESULTS

Phytocompounds and target identification

A total of 230 phytocompounds of *Vitex negundo* were identified. Of these, several compounds were found to interact with the disease targets associated with acne-causing bacteria. A total of 123 targets with a probability value greater than 0.3 were identified using the SwissTargetPrediction database. Common potential targets between the plant and the bacteria were plotted using Venny 2.1. This analysis led to the identification of 28 key targets, which were further explored. The Venn plot of the common targets is presented in Figure 1. Table 1 comprising of the phytocompounds characters from the *Vitex negundo*.

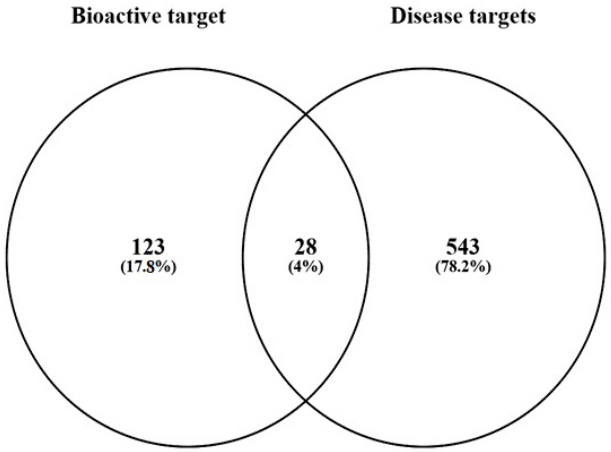

Figure 1. Venn plot for the identification of potential targets.

Network construction

The connections between the bioactive compounds of *Vitex negundo* and target genes were determined using the SwissTargetPrediction database, leveraging chemical structure similarity to predict molecular targets. Acne-related genes were sourced from GeneCards and TTD, with common targets identified using Venny 2.1, forming the foundation for network construction in Cytoscape. The network, built for key *Vitex negundo* compounds-including kaempferol, myricetin, quercetin, peroxisome proliferator-activated receptor alpha (PPARA), apigenin, and luteolin-highlighted kaempferol as the most interconnected node (degree = 18), followed by myricetin (degree = 15), quercetin (degree = 14), PPARA (degree = 11), and apigenin and luteolin (degree = 10 each). These degree values suggest their potential significance in acne treatment. Figure 2 illustrates the network, using distinct colors and shapes to enhance clarity and interpretation.

GO, pathway enrichment analysis, and protein interactions

In terms of biological processes (BP; Figure 3), the bubble plot highlights key processes with low false discovery rate (FDR) values, including inflammation regulation, lipid metabolism, and oxidative stress reduction, suggesting that *Vitex negundo* helps reduce cytokine release, balance hormonal signaling (*e.g.*, estrogen pathways), and neutralize reactive oxygen species. In addition, regarding signaling pathways (Kyoto Encyclopedia of Genes and Genomes [KEGG]; Table 2, Figure 4), the heat map produced based on the pathway enrichment analysis shows that *Vitex negundo* combats *Propionibacterium acnes* infections by modulating inflammatory responses, regulating lipid metabolism, and mitigating oxidative stress, all of which are crucial for acne management. Finally, in terms of metabolic processes (Reactome; Figure 5), the PPI network highlights key targets such as TNF, MMPs, and ESR1, indicating that *Vitex negundo* may modulate inflammatory cytokines, regulate matrix degradation enzymes, and influence hormonal pathways to prevent acne-related inflammation and skin damage.

Molecular docking

The highest binding affinity was associated with kaempferol, myricetin, quercetin, and luteolin. These ligands, along with PPARA and apigenin, were further docked using PyRx software based on their associations found in the constructed network. The best five conformations were shown by TNKS_Luteoline (Figure 6), MPO_Myrectin, MMP13_Myrectin, MMP13_Kaempferol, and MPO_Quercetin, with binding energies of -10.1, -9.5, -9.5, -9.4, and -9.2 kcal/mol, respectively.

DISCUSSION

Approximately 80% of the world's population depends on herbal remedies for disease prevention and treatment. In this study, *Vitex negundo* was analyzed for its potential use against acne vulgaris using a network pharmacology approach. A total of 230 phytocompounds were identified, of which 28 showed interactions with acne-related bacterial targets.[37,38] The network analysis identified kaempferol, myricetin, and quercetin as key compounds, with kaempferol having the highest edge count. These compounds likely modulate inflammatory responses, lipid

Table 1: Phytocompounds characters from the *Vitex negundo*

Compound name	Molecular formula	Molecular weight (kDa)	NHBA	NHBD	MlogP	DLS
Kaempferol	$C_{15}H_{10}O_6$	286.05	6	4	1.61	0.50
Myricetin	$C_{15}H_{10}O_8$	318.04	6	8	0.97	-0.24
Quercetin	$C_{15}H_{10}O_7$	302.04	7	5	1.19	0.52
Luteolin	$C_{15}H_{10}O_6$	286.05	6	4	2.78	0.38
Palmitic acid	$C_{16}H_{32}O_2$	256.24	2	1	6.64	-0.54
Pentadecanoic acid	$C_{15}H_{30}O_2$	242.22	2	1	6.13	-0.54
Stearic acid	$C_{18}H_{36}O_2$	284.27	2	1	7.65	-0.54
Lauric acid	$C_{12}H_{24}O_2$	200.18	2	1	4.62	-0.54
Arachidic acid	$C_{20}H_{40}O_2$	312.30	2	1	8.66	-0.54
Myristic acid	$C_{14}H_{28}O_2$	228.21	2	1	5.63	-0.54
beta-D-Glucose	$C_6H_{12}O_6$	180.06	6	5	-3.02	-0.12
Oleic acid	$C_{18}H_{34}O_2$	282.26	2	1	7.11	-0.30
Linoleic acid	$C_{18}H_{32}O_2$	280.24	2	1	6.60	-0.30
Linolenic acid	$C_{18}H_{30}O_2$	278.22	2	1	5.88	0.09

NHBA, number of hydrogen bond acceptors; NHBD, number of hydrogen bond donors; MlogP, Moriguchi octanol-water partition coefficient; DLS, dynamic light scattering.

Table 2: Enrichment analysis of proteins involved in acne infection

Pathway	Pathway description	Gene count	False discovery rate	Matching proteins
hsa04915	Estrogen signaling pathway	5	0.0000125	MMP2, EGFR, MMP9, SRC, ESR1
hsa04370	VEGF signaling pathway	3	0.0008700	PTK2, PTGS2, SRC
hsa04510	Focal adhesion	4	0.0012000	EGFR, PTK2, SRC, IGF1R
hsa05163	Human cytomegalovirus infection	4	0.0014000	EGFR, PTK2, PTGS2, SRC
hsa04657	IL-17 signaling pathway	3	0.0020000	MMP13, PTGS2, MMP9
hsa04625	C-type lectin receptor signaling pathway	3	0.0024000	PTGS2, SRC, SYK
hsa04670	Leukocyte transendothelial migration	3	0.0030000	MMP2, PTK2, MMP9
hsa04151	PI3K-Akt signaling pathway	4	0.0055000	EGFR, PTK2, SYK, IGF1R
hsa04921	Oxytocin signaling pathway	3	0.0059000	EGFR, PTGS2, SRC
hsa05167	Kaposi sarcoma-associated herpesvirus infection	3	0.0107000	PTGS2, SRC, SYK
hsa04015	Rap1 signaling pathway	3	0.0127000	EGFR, SRC, IGF1R
hsa00590	Arachidonic acid metabolism	2	0.0193000	PTGS2, ALOX5
hsa04144	Endocytosis	3	0.0193000	EGFR, SRC, IGF1R
hsa04664	Fc epsilon RI signaling pathway	2	0.0211000	ALOX5, SYK
hsa04917	Prolactin signaling pathway	2	0.0211000	SRC, ESR1
hsa05120	Epithelial cell signaling in Helicobacter pylori infection	2	0.0211000	EGFR, SRC
hsa05100	Bacterial invasion of epithelial cells	2	0.0217000	PTK2, SRC
hsa04064	NF-κB signaling pathway	2	0.0353000	PTGS2, SYK
hsa04066	HIF-1 signaling pathway	2	0.0353000	EGFR, IGF1R
hsa04668	TNF signaling pathway	2	0.0388000	PTGS2, MMP9
hsa05135	Yersinia infection	2	0.0461000	PTK2, SRC
hsa04068	FoxO signaling pathway	2	0.0466000	EGFR, IGF1R

MMP, matrix metallopeptidase; EGFR, epidermal growth factor receptor; SRC, SRC proto-oncogene (non-receptor tyrosine kinase); ESR1, estrogen receptor 1; PTK2, protein tyrosine kinase 2; FAK, focal adhesion kinase; PTGS2, prostaglandin-endoperoxide synthase 2; COX-2, cyclooxygenase-2; IGF1R, insulin-like growth factor 1 receptor; SYK, spleen tyrosine kinase; ALOX5, arachidonate 5-lipoxygenase.

metabolism, and oxidative stress pathways, as highlighted in enrichment analyses.[39] PPI analysis further identified targets such as TNF, MMPs, and ESR1, emphasizing the potential of *Vitex negundo* in regulating cytokine release, enzyme activity, and hormonal balance. The docking results revealed that TNKS_Luteolin exhibited the highest binding affinity (-10.1 kcal/mol), followed by MPO_Myrectin, MMP13_Myrectin,

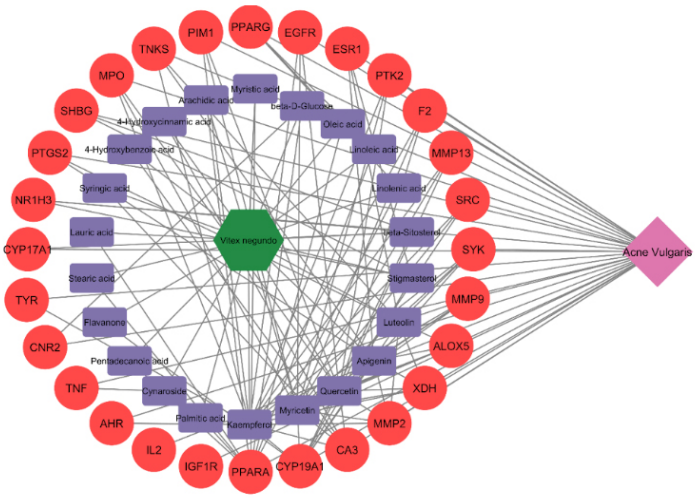

Figure 2. Network of drug-targets-disease. TNKS, Tankyrase; PIM1, Proto-Oncogene, Serine/Threonine Kinase; PPARG, Peroxisome Proliferator-Activated Receptor Gamma; EGFR, Epidermal Growth Factor Receptor; ESR1, Estrogen Receptor 1; PTK2, Protein Tyrosine Kinase 2; F2, Coagulation Factor II (Thrombin); MMP13, Matrix Metallopeptidase 13; SRC, SRC Proto-Oncogene, Non-Receptor Tyrosine Kinase; SYK, Spleen Tyrosine Kinase; MMP9, Matrix Metallopeptidase 9; ALOX5, Arachidonate 5-Lipoxygenase; XDH, Xanthine Dehydrogenase; MMP2, Matrix Metallopeptidase 2; CA3, Carbonic Anhydrase 3; CYP19A1, Cytochrome P450 Family 19 Subfamily A Member 1; PPARA, Peroxisome Proliferator-Activated Receptor Alpha; IGF1R, Insulin-like Growth Factor 1 Receptor; IL2, Interleukin 2; AHR, Aryl Hydrocarbon Receptor; TNF, Tumor Necrosis Factor; CNR2, Cannabinoid Receptor 2; TYR, Tyrosinase; CYP17A1, Cytochrome P450 Family 17 Subfamily A Member 1; NR1H3, Nuclear Receptor Subfamily 1 Group H Member 3; PTGS2, Prostaglandin-Endoperoxide Synthase 2; SHBG, Sex Hormone-Binding Globulin; MPO, Myeloperoxidase.

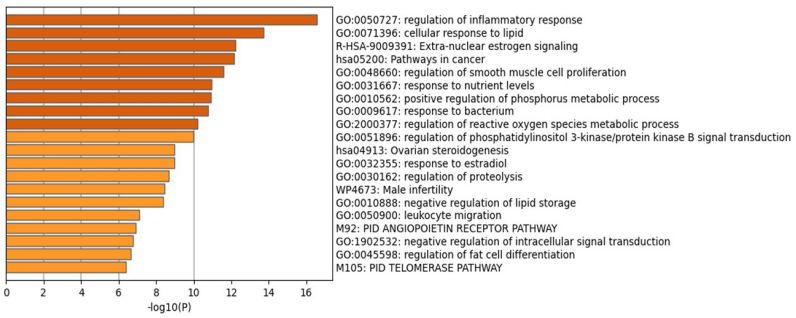

Figure 3. Heat map produced based on the path enrichment analysis. GO, gene ontology.

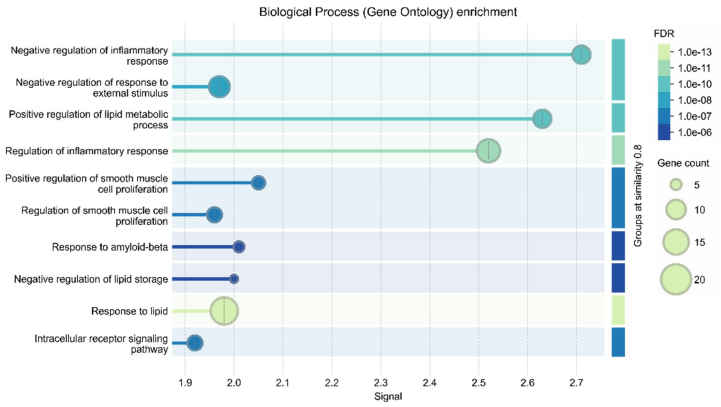

Figure 4. Biological process (gene ontology enrichment). FDR, false discovery rate.

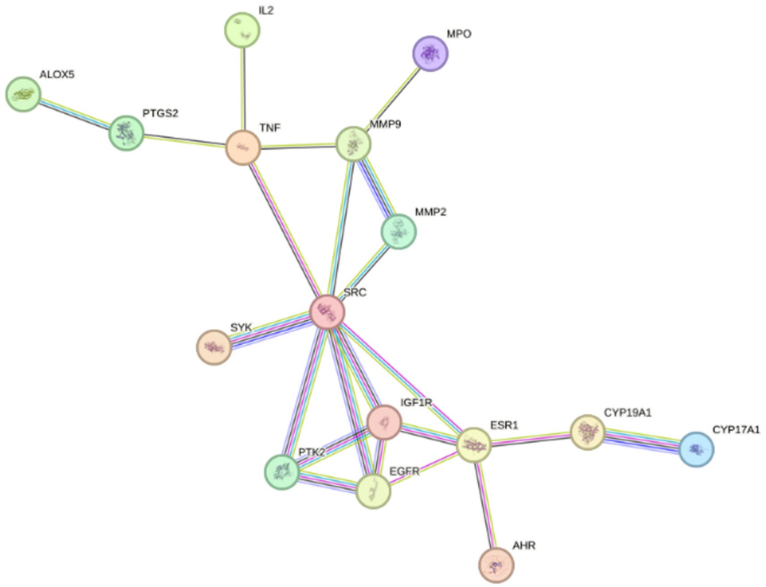

Figure 5. Network of protein–protein interactions.

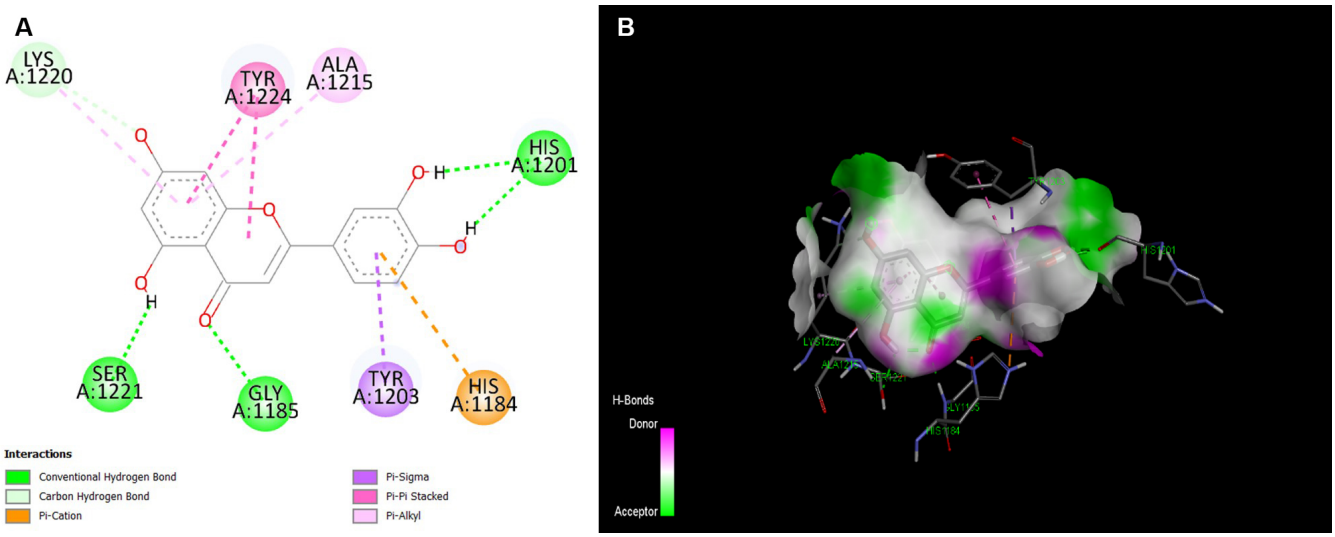

Figure 6. Molecular docking interactions of TNKS with luteolin. (A) 3D binding pose of luteolin in the TNKS active site, showing key hydrogen bonds and hydrophobic interactions. (B) 2D interaction map highlighting bonding interactions between luteolin and TNKS residues, including hydrogen bonds and π-π stacking.

MMP13_Kaempferol, and MPO_Quercetin.[40] The strong binding energies indicate a favorable interaction between these ligands and their respective targets, suggesting their potential as promising candidates for further investigation in drug development. The significant binding affinity of luteolin and myricetin highlights their role in stabilizing protein-ligand complexes, supporting their therapeutic relevance.[41,42]

CONCLUSION

This study identified 230 phytocompounds from *Vitex negundo* and explored their interactions with acne-related targets. A total of 123 targets were identified, with 28 common targets between the plant and *P. acnes*. Network analysis highlighted key compounds such as kaempferol, myricetin, and quercetin. GO and pathway enrichment revealed that *Vitex negundo* modulates inflammation, lipid metabolism, and oxidative stress, targeting key proteins such as TNF, MMPs, and ESR1. The docking results showed that TNKS_Luteolin exhibited the highest binding affinity of -10.1 kcal/mol, indicating its strong interaction with the target protein. These findings suggest that *Vitex negundo* has potential as a natural anti-

acne therapy, and further investigations are needed for formulation development.

DECLARATIONS

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Author contributions
Balekundri A: Writing and revision of the first draft. Ahire ED: English editing and proofreading. Both authors agreed on the final version and submitted the article.

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Informed consent
Not applicable.

Conflict of interest
Eknath D. Ahire is an editorial board member of the journal. The article was subject to the journal's standard procedures, with peer review handled independently of this editor and his research group.

Use of large language models, AI and machine learning tools
None declared.

Data availability statement
Supplementary data will be made available upon request.

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