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Network pharmacology and molecular docking of *Cymbopogon citratus*: Ethnomedicinal applications validation in IBS validation in IBS

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ABSTRACT

Background: *Cymbopogon citratus* (DC.) Stapf (lemongrass) is widely valued for its anti-inflammatory and antioxidant properties, but its therapeutic potential in irritable bowel syndrome (IBS) remains underexplored.

Methods: To clarify the multi-target mechanisms of *C. citratus* on IBS the integrative network pharmacology combined with molecular docking techniques were utilized. Active components were subjected to screening, then potential pharmacokinic targets were identified of which were mapped to create the Protein–Protein Interaction (PPI) networks. Key biological pathways were revealed by functional enrichment analysis through GO and KEGG, followed by the validation and KEGG, followed by the validation of compound– protein interactions through molecular docking.

Results: The five pivotal central governing hub genes were: AKT1, TNF, ESR1, EGFR, and SRC which were responsible for inflammation, epithelial window salf, and neurotransmission IBS mechanisms. From the many identified phytoconstituents, AKT1 (–10.7 kcal/mol) and EGFR (– 9.5 kcal/mol) docking analyses revealed Isoorientin and Luteolin had the strongest binding affinities, while the rest of the docking analyses revealed the strongest molecular association were through stable hydrogen bonding and hydrophobic interactions.

Conclusion: This study provides computational evidence that *C. citratus* acts through a multi- target mechanism, influencing pathways involved in IBS pathophysiology. The strong binding activity of Isoorientin and Luteolin highlights their potential as lead compounds for further pharmacological and experimental validation.

KEY WORDS

Cymbopogon citratus; Irritable bowel syndrome (IBS); Bioactive compounds; Network pharmacology; Molecular docking

ARTICLE HISTORY

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Introduction

Irritable bowel syndrome is a chronic disorder that impacts the functions of the gastrointestinal system. It typically includes clinical manifestations of abdominal pain, increased gastrointestinal discomfort, bloating, and alteration of bowel habits which includes diarrhea, constipation, or a combination of both. It constitutes one of the most common gastrointestinal conditions, with a global prevalence of 11%, although this number can vary widely due to geographic areas, dietary patterns, and diagnostic methods [1]. It predominantly impacts women and people aged 65 years and younger. The defining diagnostic criteria include pain associated with a change in the frequency or the consistency of the bowel movements and is relieved by defecation, and/or pain which is intensified by defecation [2, 3]. According to the stool consistency, IBS is divided into four groups; diarrhea-predominant IBS (IBS-D), constipation-predominant IBS (IBS-C), mixed type IBS (IBS-M), and unclassified IBS (IBS-U). IBS-D is the most common type, impacting about 40% of the population with the condition [4].

The pathophysiology of IBS remains poorly defined even though it is very common. Recent studies highlight the disorder's multifactorial nature altered Gastrointestinal (GI) motility, visceral hypersensitivity, dysbiosis, slight inflammation, and psychosocial issues [5]. A primary IBS etiology component is the disorder of the gut–brain axis. This axis includes neural,hormonal, microbial and immunological systems, and their disturbances lead to abnormal CNS processing of visceral stimuli, hypersensitivity, and the dysmotility of the gut [2, 3, 6]. The Rome IV criteria have become the standardized framework for clinical diagnosis; IBS is diagnosed based on symptoms and the organic disorders being excluded [7]. The disorder's complexity means most of the treatment is provided symptomatically and the disorder's pharmacological options are often very limited. This highlights the need for alternative or adjunctive approaches.

Another alternative for addressing digestive health is herbal medicine. One such potential candidate with ethnopharmacological history is *C. citratus* popularly known as lemongrass. It is a perennial herb that belongs to the family Poaceae. It is found in the tropical and subtropical areas of the globe especially Asia, Africa, and South America [8,9]. In terms of morphology, *C. citratus* is a tall fragrant plant with fine leaves. It is cultivated for medicine, cosmetics, and cuisine. For traditional medicine, *C. citratus* has a very wide range of application including treatment of the digestive system such as indigestion, bloating, abdominal pain, diarrhea and in the systemic medicine for tackling fever, cough, diabetes, inflammation [8, 10].

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This pharmacological action of C. *citratus* may be due to its abundant phytochemical content including essential oils, alkaloids, flavonoids, terpenoids and phenolic compounds [4, 9]. Of these, citral one of the main constituents in lemongrass essential oil (30.07–93.28%), has been largely investigated. Citral (two isomers neral and geranial) has various pharmacological effects, such as antimicrobial, antiviral, antifungal, antihyperglycemic agent, spasmolytic, anticancer and anti-inflammatory activities [11]. Various other bioactive metabolites for example β-sitosterol, quercetin, kaempferol and naringenin have exerted anti-inflammatory antioxidant and spasmolytic effects important for gut health [4, 12]. The combined effects of the compounds increase the overall biological activity of lemongrass extracts and justify their use in folk medicine.

Various research studies have examined C. *citratus* specifically for its use in gastrointestinal disorders, including IBS. Constituents of lemongrass have demonstrated spasmolytic activity on isolated intestinal tissue, indicating its potential use for intestinal spasm relief and intestinal motility disturbances associated with IBS [13, 14]. Furthermore, a processed hot-water decoction of lemongrass has been developed into a powdered concentrate for use in the management of IBS-D, traveler's diarrhea, gastroenteritis, and has been reported to provide symptomatic relief of bloating, cramping, and visceral discomfort [4]. More extensive pharmacological studies have also described the effects of lemongrass on gut inflammation, gastrointestinal motility, and gut microbiome composition, in addition to its anti-inflammatory and antioxidant activities, and its moderation of visceral pain [13, 15, 16]. These effects reflect the use of lemongrass in a more integrated approach to manage the psychological and physiological aspects of bowel disorders, as described in the previous literature [4, 9].

In recent years, the application of network pharmacology has emerged as a powerful tool for studying the multi-component, multi-target nature of herbal medicines. This approach integrates bioinformatics, systems biology, and pharmacology to elucidate the interactions between bioactive compounds, molecular targets, and disease pathways. For C. *citratus*, Fatima et al. discussed the identification of its metabolites on the network pharmacology and molecular docking studies as interacting with key proteins, IL-6, TNF, and AKT1, involved in the inflammatory regulation, gut motility, and visceral hypersensitivity. Further, the studies on molecular dynamics have contributed to understanding the therapeutic potential of the herb by demonstrating the specificity and sustained active of these compound–protein interactions. Apart from IBS, neuroprotective properties of C. *citratus* have been documented in Alzheimer's disease [17] which further expands its multi-target pharmacological profile.

Nonetheless, the combination of preclinical research and the range of pharmacological applications for C. *citratus* have not resulted in the combination of C. *citratus* into evidence- based IBS treatment. The significant diversity in extraction methods, concentrations of compounds, and clinical methods and results creates a significant barrier [18, 19]. Furthermore, comprehensive research the gaps of the mechanism for C. *citratus* demonstrates a need for a more thorough bridge between ethnopharmacological research and contemporary synergistic methods of research.

Therefore, the present study aims to employ network pharmacology, molecular docking, and bioinformatics-based analyses to systematically explore the therapeutic potential of C. *citratus* in IBS. By integrating compound–target predictions, signaling pathway analyses, and protein– ligand interaction simulations, this work seeks to validate the ethnomedicinal applications of lemongrass in IBS management and provide mechanistic insights to support its use in contemporary evidence-based medicine.

Materials and Methods

Screening of bioactive phytochemicals of *C. citratus*

Information about the chemical compounds was collected from earlier research papers and reliable online sources such as Dr. Duke's Phytochemical and Ethno-botanical Database https://phytochem.nal.usda.gov/phtochemical/ search [20] and the Indian Medicinal Plants, Phytochemistry and Therapeutics (IMPPAT) database https://cb.imsc.res.in/imppat/ [21]. To identify the most promising bioactive compounds, the Traditional Chinese Medicine Systems Pharmacology (TCMSP) platform https://tcmsp-e.com/tcmsp.php was used. Compounds were chosen based on two key properties oral bioavailability (OB) above 20% and drug-likeness (DL) higher than 0.10 [22]. Oral bioavailability (OB) pertains to the extent and rate at which a substance is absorbed and becomes available to the target tissues after administration by the oral route; and dose-likeness (DL), refers to the extent to which the compound resembles an actual marketed drug in terms of its structural and functional chemistry. These two parameters conjointly aid in estimating the potential of a compound in the formulation of a viable therapeutic agent [23].

Target Identification of bioactive compounds from *C. citratus*

The Swiss Target Prediction tool available at http://www.swisstargetprediction.ch/ was used to determine the possible target genes for bioactive compounds from C. *citratus*. Each compound's chemical structures were accessed in the SMILES format. Each analysis was confined to the genes of the species Homo sapiens [24]. Only those targets whose prediction score was 0.7 or higher were taken for subsequent evaluation. Removal of duplicated genes was done through cross-verification of the UniProt IDs within the UniProtKB database at https://www.uniprot.org/help/uniprotkb.

Identification of disease-associated targets

Genes related to irritable bowel syndrome were obtained from DisGeNET https://disgenet.com/ and Gene Cards https://www.genecards.org/ using the query "irritable bowel syndrome." These databases inform on the role different genes play on the pathogenesis of IBS and aids in narrowing down genes which could be the primary drivers of the disease. To eliminate duplicate records, the UniProt database https://www.uniprot.org/help/uniprotkb . UniProt IDs were used to match records.

Integration of compound and disease targets

The predicted targets of C. citratus bioactive compounds were compared with the disease associated genes to identify overlapping targets. These common genes were considered potential molecular points where C. *citratus* could exert therapeutic effects against IBS, forming the basis for subsequent network pharmacology and molecular docking analyzes.

Construction of venn diagrams

To identify and visualize the shared potential target genes of C. *citratus* against irritable bowel syndrome (IBS), the online tool Venny 2.1.0

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https://bioinfogp.cnb.csic.es/tools/venny/index.html was used. A Venn diagram was generated to illustrate the overlapping genes between the bioactive compounds of *C. citratus* and the disease associated targets, highlighting the common targets that may play a key role in the therapeutic effects of the plant against IBS.

Construction of compound target network

Utilizing Cytoscape v3.10.3 (https://cytoscape.org/), a compound target network was constructed for the purpose of visualizing the relationships between the bioactive compounds of lemongrass and their protein targets. Active compounds and target genes were represented by nodes and their interactions were represented by edges. Key bioactive compounds or important target proteins possessing many connections are represented by larger nodes [25].

Protein–protein interaction (PPI) network

The intersecting targets identified from Venn analysis were input into the STRING database https://string-db.org/ to obtain a protein–protein interaction network, using a confidence score threshold of 0.7. The resulting network was visualized in Cytoscape, and isolated nodes were removed to simplify interpretation. Hub genes were identified using the CytoHubba plugin in Cytoscape, which ranks nodes based on their degree of connectivity. Highly connected proteins such as TNF, SRC, EGFR, AKT1, and ESR1 were identified as key regulators potentially modulated by lemongrass compounds in IBS.

Gene ontology (GO) and KEGG pathway analysis

Functional classification as well as pathway enrichment analyses of shared target genes were accomplished through ShinyGO v0.77 (https://bioinformatics.sdstate.edu/go/) and Reactome (https://reactome.org/). The analyses were primarily centered on the BP (Biological Process), MF (Molecular Function), and CC (Cellular Component) domains of the Gene Ontology. In addition, we carried out KEGG pathway enrichment analyses to characterize the primary signaling pathways related to IBS and specifically those that involve intestinal inflammation, neurotransmission, smooth muscle contraction, and immune regulation. We used a threshold of $p< 0.05$ to determine statistical significance [26].

Molecular docking studies

Molecular docking was used to predict and assess the interactions between the bioactive compounds obtained from *C. citratus* and the central target proteins for irritable bowel syndrome (IBS). The bioactive compounds were obtained through screening and the core proteins were obtained through the PPI networks which were built in Cytoscape. Phytochemical 3D molecular structures were obtained from the PubChem database and converted to PDB format through Open Babel v3.1.1 software. Also, the target proteins corresponding to the hub genes were obtained from the RCSB database. These proteins were then prepared for docking by removing water molecules, co-crystallized ligands, and other heteroatoms as well as adding hydrogen atoms to the structure for molecular stability. The edited structures were saved in PDBQT format for docking.

Docking was performed using the AutoDock Vina v1.2.0 [27]. A grid box for each protein was created and centered over the active site for each protein as described in the literature. After docking, the ligand protein complexes were ranked based on their docking scores. The most favorable complexes were used for further studies in Discovery Studio Visualizer, where molecular interactions were characterized to understand protein–ligand interactions, and inter and intramolecular interactions (such as hydrogen bonds, van der Waals, and hydrophobic interactions).

Results and Discussions

Screening of bioactive compounds of *C. citratus*

Based on the TCMSP data for *C. citratus*, eleven bioactive compounds met both of the pharmacokinetic requirements (oral bioavailability OB ≥ 20% and drug-likeness DL ≥ 0.10) as recommended in a previous study [23]. Of the compounds evaluated, (-)-Globulol (OB = 85.51%, DL = 0.12) and Spathulenol (OB = 82.33%, DL = 0.12) possessed the highest oral bioavailability suggesting strong absorption potential and positive pharmacokinetic disposition. Isoorientin (OB = 23.3%, DL = 0.76) achieved highest drug-likeness suggesting stably and structurally compatible integration into a biological system, and higher biological system circulation. Luteolin (OB = 36.16%, DL = 0.25) and Caryophyllene oxide (OB = 35.94%, DL = 0.13) also demonstrated adequate pharmacokinetic profiles suggesting their potential for drug development and synthesis.

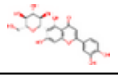
TCMSP-based screening confirms that *C. citratus* comprises a wider assortment of pharmacologically interesting flavonoids and terpenoids with favorable ADMET characteristics. The high OB of (-)-Globulol and Spathulenol and the high DL of Isoorientin and Luteolin make these compounds the most noteworthy. This is consistent with the compound selection approach detailed by Subba et al. [23] further corroborating the applicability of TCMSP parameters in determining highly promising lead candidates from ADMET analysis among plant constituents within traditional medicine.

Target prediction of *C. citratus* against irritable bowel syndrome (IBS)

A total of 338 potential target genes were identified for the bioactive compounds present in *C. citratus* using a probability threshold greater than 0.04. Meanwhile, 5,488 disease- related genes associated with irritable bowel syndrome (IBS) were obtained from databases such as DisGeNET and GeneCards. To identify the most relevant therapeutic targets, both gene sets were compared using the Venny 2.1.0 online tool.

As shown in the Venn diagram (Figure 1), 278 overlapping genes were found between *C. citratus* and IBS. These common genes represent the potential molecular targets through which *C. citratus* may exert its therapeutic effects on IBS. Consequently, these shared targets were selected for further network construction and pathway enrichment analysis to explore their biological significance and pharmacological mechanisms (Table 1).

Table 1. Major phytochemicals of *Vitex negundo* showing OB > 20% and DL > 0.20 along with their characteristics and 2D structures.

Sl. No.	Chemical Name	Mol. Formula	Mol. Weight (g/ml)	OB %	DL	2D structure	Pub Chem ID
1.	Isoorientin	C21H20O11	448.41	23.3	0.76		114776

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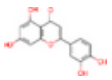
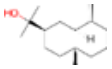
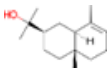
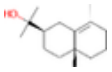
2.	Isoorientin	C15H10O6	286.25	36.16	0.25		5280445
3.	beta-Cubebene	C15H24	204.39	32.81	0.11		93081
4.	Spathulenol	C15H24O	220.39	82.33	0.12		92231
5.	beta-Eudesmol	C15H26O	222.41	26.09	0.10		91457
6.	alpha-Eudesmol	C15H26O	222.41	25.02	0.10		92762
7.	Humulene epoxide II	C15H24O	220.39	33.23	0.10		10704181
8.	Oleic acid	C18H34O2	282.52	33.13	0.14		445639
9.	gamma-Eudesmol	C15H26O	222.41	24.28	0.10		6432005
10.	Caryophyllene oxide	C15H24O	220.39	35.94	0.13		1742210
11.	(-)-Globulol	C15H24O	222.41	85.51	0.12		12304985

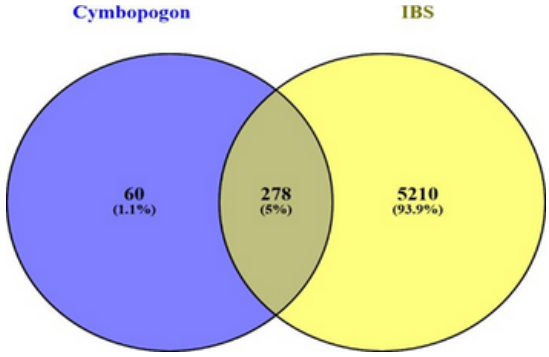


Figure 1. Venn diagram showing common target genes between *C. citratus* bioactive compounds and irritable bowel syndrome (IBS).

Construction of compound–target network

To investigate how bioactive compounds from *C. citratus* interact with proteins connected to IBS, we designed a compound–target network. This network was constructed in Cytoscape and included 11 active compounds, a few of which are Luteolin, β-Eudesmol, Caryophyllene oxide, and Oleic acid, which connected to a significant number of protein targets (green nodes) to create a richly connected network. The clusters of nodes are closely packed which indicates that many of these interactions are molecular in nature and that several of the compounds may have multitarget characteristics which integrate to the overall therapeutic value of *C. citratus*. Furthermore, Luteolin and β-Eudesmol in particular had a large number of connections which demonstrates that they are likely to influence the primary pathways that are altered in IBS (Figure 2).

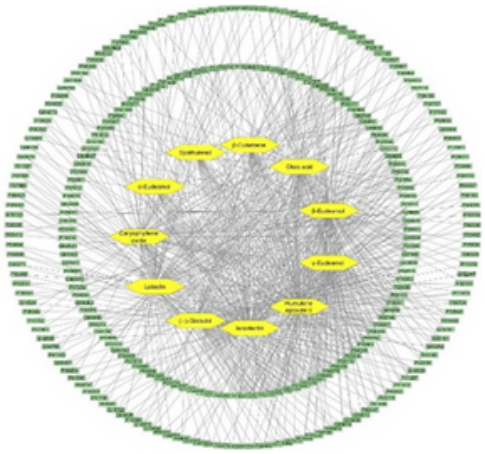


Figure 2. Compound–Target Interaction Network of 11 targetcompounds and 278 target genes.

Interaction network of Cymbopogon bioactive and IBS-related targets

A total of 278 overlapping genes were identified between *C. citratus*, bioactive targets and irritable bowel syndrome (IBS)–related genes (Figure 3). These genes were analyzed using the

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STRING database to construct a protein–protein interaction (PPI) network (Figure 3A & E). The resulting network comprised 275 nodes and 3237 edges, indicating a highly interconnected structure. The dense arrangement of nodes suggests that the overlapping targets are closely associated, implying that C. *citratus*, may influence IBS through multiple molecular mechanisms and pathways.

To pinpoint the most influential genes within the network, hub gene analysis was performed in Cytoscape using the degree centrality method. Based on their degree, and MNC values, the top five hub genes were identified as AKT1, TNF, ESR1, EGFR, and SRC whereas through the MCC values the five hub genes identified were AKT1, MDM2, TNF, ESR1, and HIF1A (Figures 3 B–D). These genes exhibited the highest interaction degrees, indicating their essential regulatory roles within the PPI network.

Each core gene carries its own separate function while also being interconnected. AKT1 is a pivotal regulator of cell inflammation and survival [28]. TNF is an important inflammatory cytokine and contributes to the inflammation immune dysregulation [29]. ESR1 (estrogen receptor alpha) is associated with the control of gut motility [30]. EGFR facilitates repair and regeneration of the epithelium [31]. Lastly, SRC is a signaling kinase that facilitates the cross- talk of several pathways [28]. The proximity and co-function of these genes is a testament that C. *citratus*, may induce pro-therapeutic effects by simultaneous inflammatory, hormonal, and restorative signaling pathways.

Overall, the combined PPI and hub gene analyses demonstrate that C. citratus potentially acts through multi-target modulation, primarily centered on these five key hub genes that govern critical biological processes involved in IBS pathophysiology.

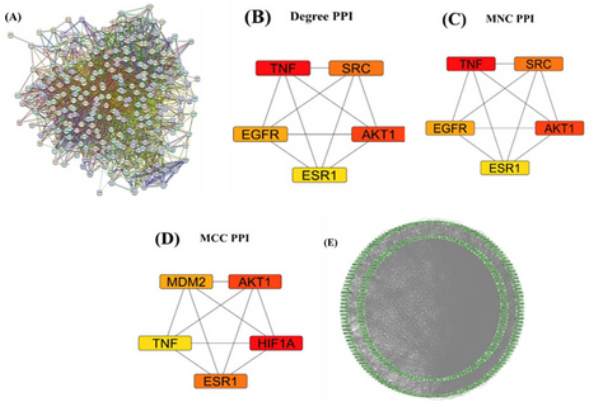

Figure 3. (A) Protein–protein interaction (PPI) network of overlapping targets between C. citratus bioactive compounds and irritable bowel syndrome (IBS)–associated genes constructed using the STRING database. (B) The PPI network optimized through Degree method. (C) The PPI network optimized through MNC Degree method. (D) The PPI network optimized through MCC method. The network revealsstrong interconnectivity among 278 shared genes, suggesting complex molecular associations. (E) Illustrates the overall PPI framework, highlighting the dense and integrated interaction patterns among the target proteins.

GO and KEGG pathway enrichment analysis

In order to identify the biological importance of the overlapping targets, Gene Ontology (GO) and KEGG enrichment analyses were studied. In the GO Biological Process (BP) category (Figure 4A), the most relevant enriched terms involved the processes of 'cellular response to nitrogen compound ,' 'synaptic signaling,' and 'chemical synaptic transmission'. These were indicative of possible inflammatory and neuronal regulation functions. Regarding the prespecified GO Cellular Component (CC) (Figure 4B), analyses indicated that most of the target genes were located within the presynaptic membrane, membrane raft, and postsynaptic membranes. This indicates contributions to functions of membrane signaling. In the GO Molecular Function (MF) (Figure 4C), the most important enriched terms were 'G protein– coupled amine receptor activity,' 'nuclear receptor activity,' and 'kinase activity,' signaling multifunctional control, regulation, and possible 'signaling' functions. In the KEGG pathway analysis (Figure 4D), the most significant enriched pathways were 'VEGF signaling,' 'steroid hormone biosynthesis,' 'neuroactive ligand–receptor interaction,' and 'inflammatory mediator regulation of TRP channels.' Each of which pertains to the potential pathophysiology of irritable bowel syndrome (IBS).

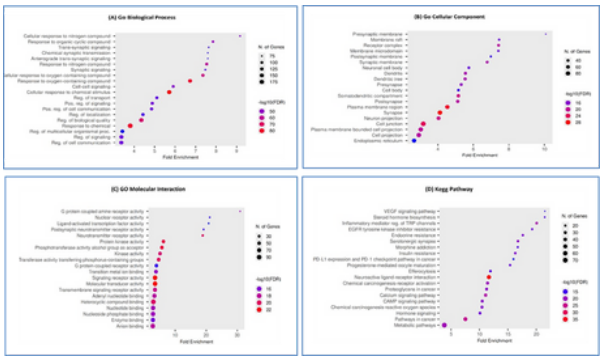

Figure 4. Bubble map of enrichedgene functions and pathways of C. *citratus* targets, including (A) GO Biological Processes, (B) GO Cellular Components, (C) GO MolecularFunctions, and (D) KEGG pathways.

The KEGG pathway analysis revealed that several overlapping target genes are involved in the serotonergic synapse pathway, which plays an important role in regulating mood, gut movement, and communication between nerve cells. As shown in Figure 5, key genes such as 5-HT2A (HTR2A), SERT (SLC6A4), PKC, ERK, and MAO-A were significantly enriched in this pathway. These genes are responsible for serotonin release, transport, and signaling across synapses. Their activation suggests that C. *citratus* bioactive compounds may influence serotonin balance and neuronal communication, which could help relieve irritable bowel syndrome (IBS) symptoms through the gut–brain axis.

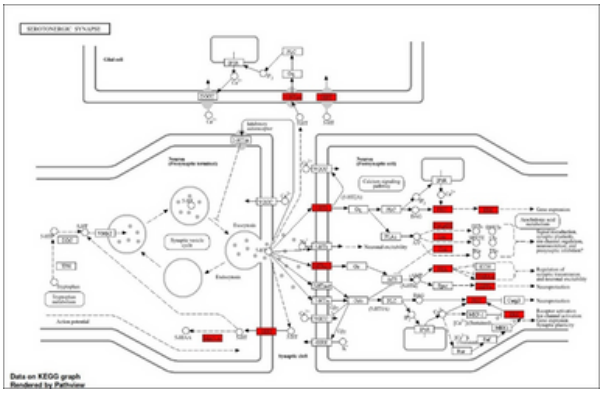

Figure 5. Potential targets and mechanisms of bioactive compounds from C. *citratus* in IBS, highlighting pathways involved in serotonergic synapse pathway.

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Reactome pathway enrichment analysis

According to pathway enrichment analysis by Reactome, overlapping target genes were predominantly linked to biological activities such as signal transduction, immune system response, and metabolism. The Reacfoam Map (Figure 6) pointed to and described the target genes in the major biological systems linked to immune system, developmental biology, hemostasis and response to cellular stress, suggesting the target genes have wide biological importance.

Figure 6. Reacfoam map enrichment analysis of *C. citratus* induced pathways.

Targeted visualization of genes in specific signaling pathways also showed enrichment of the GPCR signaling pathways, particularly G alpha (Q), G alpha (S), and G alpha (I) pathways (Figure 7A), which are central to gut motility and neurotransmission. Also enriched were interleukin signaling pathways suggesting immune and inflammatory response modulation and cellular signaling of the IL-2, IL-4, IL-6, and IL-10 families (Figure 7B).

Moreover, pathways related to cholesterol and steroid metabolism (Figure 7C) were found to be significantly enriched, pointing toward the regulation of lipid homeostasis and hormone biosynthesis. Together, these findings suggest that *C. citratus* bioactive compounds may exert therapeutic effects on irritable bowel syndrome (IBS) through multiple mechanisms balancing immune function, modulating neurotransmitter signaling, and maintaining metabolic stability. The details of top ten enriched pathways observed through Reactome is also shown in Table 2.

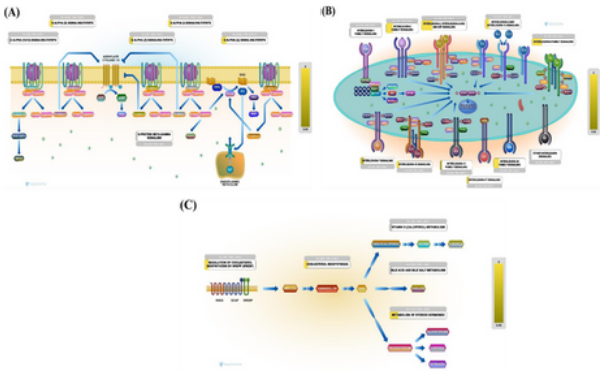

Figure 7. Reactome pathway enrichment of overlapping genes showing involvement in (A) GPCR signaling pathways, (B) interleukin signaling pathways, and (C) metabolism of steroids pathways.

Table 2. Top 10 enriched reactome pathways.

Rank	Pathway ID	Pathway Name	p-Value
1	R-HSA-162582	Signal Transduction	1.11E−16
2	R-HSA-372790	Signaling by GPCR	1.11E−16
3	R-HSA-388396	GPCR downstream signaling	1.11E−16
4	R-HSA-556833	Metabolism of lipids	1.11E−16
5	R-HSA-373076	Class A/1 (Rhodopsin-like receptors)	1.11E−16
6	R-HSA-1430728	Metabolism	1.11E−16
7	R-HSA-500792	GPCR ligand binding	1.11E−16
8	R-HSA-112316	Neuroactive ligand-receptor interaction	1.11E−16
9	R-HSA-500792	Peptide ligand-binding receptors	1.11E−16
10	R-HSA-164952	G alpha (i) signaling events	1.11E−16

Molecular docking analysis

From the network analysis, five key hub genes AKT1, TNF, ESR1, EGFR, and SRC were identified based on their strong interaction scores and central positions within the protein–protein interaction (PPI) network. These genes are known regulators of critical cellular processes such as growth, survival, and apoptosis, and their dysregulation has been closely linked to cancer progression. Considering their biological importance, these hub genes were selected for molecular docking analysis to investigate their binding interactions with major *C. citratus* - derived phytochemicals.

According to the results of molecular docking (Table 3), Isoorientin and Luteolin exhibited strong and consistent affinities with two of the most important hub proteins, AKT1 and EGFR, indicating possible their possible roles in the modulation of cancer pathways. Isoorientin had the highest binding affinity with AKT1 (PDB ID: 3O96) of −10.7 kcal/mol and Luteolin followed with −9.8 kcal/mol. Isoorientin also recorded a binding energy of −9.5 kcal/mol with strong interaction with EGFR (PDB ID: 1M17).

Table 3. Binding affinities (kcal/mol) of Cymbopogon-derived phytochemicals with hub proteins.

SI. No.	Ligands	Hub genes - Binding affinities (kcal/mol)				
		TNF	SRC	EGFR	AKT1	ESR1
1	Isoorientin	-6.1	-9.0	-9.5	-10.7	-5.8

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2	Luteolin	-5.9	-9.0	-8.8	-9.8	-8.5
3	beta-Cubebene	-5.6	-7.5	-6.9	-8.6	-7.6
4	Spathulenol	-5.6	-7.3	-7.5	-8.2	-7.8
5	beta-Eudesmol	-6.3	-7.5	-7.7	-8.0	-7.7
6	alpha-Eudesmol	-6.0	-7.4	-7.7	-8.3	-7.7
7	Humulene epoxideII	-5.3	-6.6	-6.8	-7.2	-7.9
8	Oleic acid	-4.2	-6.3	-5.6	-6.9	-6.3
9	gamma-Eudesmol	-6.1	-7.2	-7.4	-8.5	-7.7
10	Caryophyllene oxide	-5.4	-7.1	-6.8	-7.6	-8.1
11	(-)-Globulol	-5.7	-7.4	-7.1	-8.4	-8.0

This was also evident in the analyses of hydrogen bonds and hydrophobic interactions. The Isoorientin–AKT1 complex established hydrogen bonds with ASN54, SER205, and TYR272 and formed hydrophobic interactions with TRP80, VAL270, and LYS268, indicating stable and appropriately oriented binding in the active site of AKT1. Likewise, hydrogen bonds formed by the Luteolin–AKT1 complex with SER205 and THR211, and the hydrophobic contacts with LEU264, TRP80, LEU210, VAL270, and associated with hydrophobic TRP80, confirm its stability in the kinase pocket (Table 4).

In the Isoorientin–EGFR complex, multiple hydrogen bonds were formed with LYS721, THR830, ASP831, ALA719, GLU738, THR766, and PRO770, along with hydrophobic interactions involving VAL702, LEU694, ALA719, and LEU820, indicating a highly stable and specific binding configuration.

Table 4. Detailed interaction residues of top compounds (Isoorientin and Luteolin) with AKT1 and EGFR.

Sl. No	Ligands	Hub Genes	Binding affinities (kcal/mol)	Hydrogen Bond	Hydrophobic interactions
1	Isoorientin	AKT1(PDB ID:3O96)	-10.7	ASN54, SER205, TYR272	TRP80, VAL270, LYS268
2	Luteolin	AKT1(PDB ID:3O96)	-9.8	SER205, THR211	LEU264, TRP80, LEU210, VAL270
3	Isoorientin	LEU210, VAL270 -9.5 (PDB ID: 1m17)	-9.5	LYS721, THR830, ASP831, ALA719, GLU738, THR766, PRO770	VAL702, LEU694, ALA719, LEU820

The 2D and 3D interaction visualizations (Figure 8A-8C) clearly depict the docking orientations and bonding patterns of Isoorientin and Luteolin within the active sites of AKT1 and EGFR. The recurring formation of hydrogen and hydrophobic interactions across these complexes highlights their strong and stable affinities, with Isoorientin exhibiting slightly superior binding efficiency compared to Luteolin.

Overall, these findings demonstrate that Cymbopogon compounds, particularly Isoorientin and Luteolin, can effectively interact with major signaling proteins such as AKT1 and EGFR, supporting their potential role as multitarget therapeutic agents in cancer modulation.

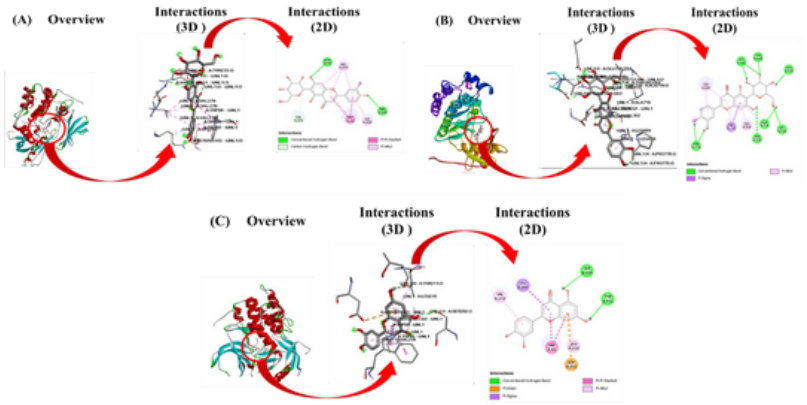

Figure 8. The top 3 molecular docking interactions of key phytochemical compunds with the hub proteins. (A) Interaction of AKT1 (PDB ID: 3O96) with Isoorientin (PubChem ID: 114776), (B) Interaction of EGFR (PDB ID: 1M17) with Isoorientin (PubChem ID: 114776), and (C) Interaction of AKT1 (PDB ID: 3O96) with Luteolin (PubChem ID: 5280445).

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Conclusion

This research utilized an integrative technique to merge network pharmacology with molecular docking to analyze the therapeutic possibilities of *C. citratus* for irritable bowel syndrome (IBS). In the network-based study, AKT1, TNF, ESR1, EGFR, and SRC were introduced as the five major hub genes linked to the signaling pathways of IBS. These targets have been identified as major actors of inflammation, epithelium, and neurotransmission, all of which play a critical role in IBS.

Among the studied compounds, Isoorientin and Luteolin showed the most promising interactions, with particularly strong and stable binding affinities with AKT1 and EGFR. As indicated in the docking analysis, the observed hydrogen bonding as well as the hydrophobic and van der Waals interactions are a strong indication of the ability of these compounds to bind within the active site pocket of the target proteins, which signals the ability of these compounds to regulate molecular pathways such as PI3K/AKT and EGFR.

The findings align with earlier reports on the anti-inflammatory, antioxidant, and smooth muscle–relaxant qualities of *C. citratus*. These qualities may contribute to the alleviation of IBS symptoms. Furthermore, the diverse and multi-targeted nature of these interactions seems to reinforce the hypothesis that natural plant materials operate via network-based mechanisms, affecting numerous systems at once rather than single molecular targets.

Hence, the results from the current study provide strong computational affirmation that the bioactive constituents Isoorientin and Luteolin of *C. citratus* are anti-inflammatory, act on interoceptive hormonal mechanisms, and modify neural pathways. Results confirm its use in traditional medicine and provide a scientific rationale to pursue additional in vitro, in vivo, and clinical studies to ascertain the safety and confirm the pharmacological effects of *C. citratus* on IBS.

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Competing and Conflicting Interests

The authors declare that they have no conflict of interest.

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