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Multi-Target Anti-Obesity Mechanisms of *Pedalium murex* Mucilage: A Cheminformatics and Network Pharmacology Study

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ABSTRACT

Obesity is a global epidemic challenge with significant comorbidity-associated health risks, psychological implications, and economic burden. The inefficiency and side effects of current therapeutics highlight the necessity for safer alternative therapeutics and multi-target therapeutic strategies. *Pedalium murex* L., a plant used in culinary and medicinal practices across many cultures globally, has shown potential anti-obesity effects. This study used cheminformatics and network pharmacology to identify anti-obesity bioactive compounds in *P. murex* mucilage and understand their mechanism of action. Three key antiobesity compounds in *P. murex* mucilage, viz. 3-Oxo-12,18-ursadien-28-oic acid, Epifisetinidol-(4β→8)-catechin, and Moschamine were recognized and analysed for their anti-obesity properties and obesity pathway modulations. These compounds were shown to target 300 potential human targets, including PPARG, FASN, and UCP-1, which are key regulators of adipogenesis, lipogenesis, and thermogenesis. Network pharmacology revealed their involvement in lipid metabolism and the inflammatory response, highlighting their polypharmacological mode of action. This study provides evidence that *P. murex* mucilage bioactives have multi-target anti-obesity effects through the modulation of metabolic and inflammatory pathways, suggesting its potential as natural anti-obesity therapeutics.

INTRODUCTION

Obesity has emerged as a global health epidemic, hurting over 2.5 billion adults worldwide with significant comorbidities and substantial socioeconomic impacts (WHO, 2023; Geng et *al.*, 2022; Muscogiuri *et al.*, 2022; Rubinstein *et al.*, 2021). While current pharmacotherapies show limited efficacy and adverse effects (Srivastava *et al.*, 2023), traditional medicinal plants offer promising alternatives, with 80% of developing populations relying on herbal remedies for primary healthcare (Zhao *et al.*, 2022; Tamang *et al.*, 2023). Traditional and contemporary pharmacological studies proved that medicinal plants are rich sources of bioactive compounds with multifaceted effects, including modulation of adipogenesis (Rayalam *et al.*, 2008), inflammation (Pan *et al.*, 2016), and lipid metabolism (Yang *et al.*, 2016). Among the 70,000 recognised medicinal species (Devanesan *et al.*, 2018), *Pedalium murex* L. (commonly known as Indian Gohra or Yaanainerinji in classical Tamil) stands out for its extensive therapeutic applications in traditional Indian systems such as Ayurveda and Siddha. It has been widely used to manage diabetes, inflammatory conditions, and urinary disorders (Ramadevi *et al.*, 2020), positioning it as a promising candidate for multi-target anti-obesity therapy. Earlier work from our laboratory has established the anti-obesity potential of mucilage derived from the leaves of *P. murex* (Jeyakumar *et al.*, 2024). Despite this documented bioactivity and its expected polypharmacological properties, the precise molecular mechanisms underlying its anti-obesity effects have yet to be elucidated and hence remain unexplored.

The current study examines the *P. murex*'s anti-obesity potential due to its rich phytochemical profile comprising flavonoids, phenolics and triterpenoids (Madasamy *et al.*, 2023; Ram *et al.*, 2021) through investigating how these phytomolecules control obesity by analysing their biochemical pathways. Using an integrated cheminformatics and network pharmacology approach, three important anti-obesity compounds were identified in *P. murex* mucilage: 3-Oxo-12,18-ursadien-28-oic acid, Epifisetinidol-(4ß→8)-catechin, and Moschamine. This study intends to study the *P. murex* phytocompounds' anti-obesity properties through characterizing their interactions with key human targets-PPARG (adipogenesis), FASN (lipogenesis), and UCP-1 (thermogenesis) (Han *et al.*, 2022). Through

integrated Gene Ontology mapping and network pharmacology approaches, current research aims to systematically elucidate: (1) their modulation of lipid metabolism and inflammatory pathways, and (2) their polypharmacological mechanisms of action (Bultum *et al.*, 2022; Liu *et al.*, 2024). This study aims to combine traditional Indian medicinal knowledge with modern cheminformatics and network pharmacology to explore the anti-obesity mechanisms of *P. murex* mucilage phytocompounds. It intends to characterise the polypharmacological action of these bioactive on key obesity-related targets and pathways, evaluating target selectivity and potential off-target effects.

2. Materials and methods

2.1 Selection of *P. murex* Mucilage Bioactive Phytocompounds

Current research selected three promising anti-obesity bioactive *P. murex* mucilage compounds for further study based on computational analyses. The compounds showed superior pharmacological potential including Epifisetinidol-(4β→8) catechin, Moschamine, and 3-Oxo-12,18-ursadien-28-oic acid were selected and included in the study. Their properties and structures are detailed in Table 1.

S.No	Compounds name	IUPAC Name	Canonical SMILES
1	Epifisetinidol(4beta>8) catechin	2-(3,4-dihydroxyphenyl)-8-[2-(3,4-dihydroxyphenyl)-3,7-dihydroxy-3,4-dihydro-2H-chromen-4-yl]-3,4-dihydro-2H-chromene-3,5,7-triol	C1C(C(OC2=C1C(=CC(=C2C3C(C(OC4=C3C=CC(=C4)O)C5=CC(=C(C=C5)O)O)O)O)O)C6=CC(=C(C=C6)O)O)O
2	Moschamine	(E)-N-[2-(5-hydroxy-1H-indol-3-yl)ethyl]-3-(4-hydroxy-3-methoxyphenyl)prop-2-enamide	COC1=C(C=CC(=C1)/C=C/C(=O)NCCC2=CNC3=C2C=C(C=C3)O)O
3	3-Oxo-12,18-ursadien-28-oic acid	1,2,6a,6b,9,9,12a-heptamethyl-10-oxo-2,3,4,5,6,6a,7,8,8a,11,12,13-dodecahydropicene-4a-carboxylic acid	CC1CCC2(CCC3(C(=CCC4C3(CCC5C4(CCC(=O)C5(C)C)C)C)C2=C1C)C)C(=O)O

Table 1: *P. murex* selected compound's properties

This targeted selection approach allows us to focus on investigating the most therapeutically relevant components while capturing the phytochemical diversity of *P. murex* mucilage.

2.2 Compound Characterization and Validation

The three selected *P, murex* mucilage bioactive compounds were structurally characterized by means of an integrated bioinformatics approach. The carried workflow comprised (1) the Compound-Specific Data Retrieval from PubChem using the following PubChem Compound Identifiers CID 131751381 (Epifisetinidol-(4β→8)-catechin), CID 5318993 (Moschamine), CID 12308714:(3-Oxo-12,18-ursadien-28-oic acid). Each compound's IUPAC names and common synonyms, molecular formulas and weights, 2D and 3D structural fingerprints in SDF, experimental physicochemical properties, and their predicted ADMET properties including LogP values and number of hydrogen bond donor/acceptor were retrieved. The collected structural data were subjected rigorous validation multi-level structural validation by InChIKey verification, mass spectrometry data matching, and comprehensive literature cross-referencing, the data's quality was assured SMILES consistency and 3D conformation validation (Liu *et al.*, 2025).

2.3 Human Target Prediction and Validation

The potential antiobesity human targets of the selected *P. murex* mucilage three bioactive compounds were predicted using Swiss Target Prediction (version 2023.02) by entering the human canonical SMILES strings alongside a >0% probability threshold, using a combined 2D/3D similarity method that integrated energy-minimized 3D conformers, molecular fingerprint/shape-based cross-validation, and experimental evidence-based filtering, with confidence scores derived from pharmacophore similarity, binding site complementarity, and known ligand-target interactions. Predicted targets were then annotated employing Expression Atlas (release 48), concentrating on tissue-specific expression and obesity-related differential expression, whereas the chromosomal locations, protein-protein interactions, and pathway enrichments were methodically retrieved. Comprehensive target characterization was accomplished by means of UniProtKB (2023_03) for functional domains/post-translational modifications and chromosomal analysis for GWAS obesity hotspots and synteny conservation), followed by rigorous quality control. The refined target list was finally subjected to integrated analysis including GO/KEGG pathway mapping, obesity association scoring, and network topology assessment for ensuring robust multi-criteria prioritization of obesity-relevant targets (Muthuramalingam *et al.*, 2017).

2.5 Gene Ontology (GO) Enrichment Analysis

GO analysis was carried out using GOnet (v2.0) with curated HGNC-approved gene symbols against the human genome background, incorporating orthology validation. The current analysis executed the multi-level mapping of lipid homeostasis, metabolic regulation, inflammatory response, etc., like obesity associated biological processes, receptor binding, enzyme inhibition, transporter activity like molecular functions, and cellular components, with statistical significance. Outcomes were validated through STRING DB (v12.0) network analysis and manual literature curation, visualized via REVIGO semantic similarity and ggplot2 heatmaps (R v4.3.1), with quality control including GOSemSim redundancy reduction, GTEx v8 tissue-specific expression verification, and KEGG pathway coherence confirmation.

2. 6 Compound-Target Network (C-T-N) Pharmacology Construction and Analysis

The C-T-N was constructed using Cytoscape (v3.9.1) with the following careful workflow: (1) Network generation where nodes corresponding to either compounds or human targets, with edges weighted by binding affinity and prediction confidence scores (SwissTargetPrediction probability ≥30%), have as a feature only experimentally validated interactions from STITCH (v5.0) and Binding DB; (2) Topological analysis calculating node degree, betweenness centrality, and clustering coefficients by means of Network Analyzer, with key hub targets acknowledged as those in the top 90th percentile for both degree and centrality; (3) Functional module detection through MCODE (v2.0.2) with parameters: degree cutoff=5, node score cutoff=0.4, k-core=4, max depth=100; and (4) Polypharmacological profiling that quantified multi-target activity through Shannon entropy scoring of target class distributions, followed by pathway enrichment analysis of modular targets using ClueGO (v2.5.9) with right-sided hypergeometric testing. The integrated analytical pipeline included quality control steps together with target-disease association validation through DisGeNET (v7.0) and expression profiling in metabolic tissues to ensure biological relevance to obesity pathophysiology.

3. Results

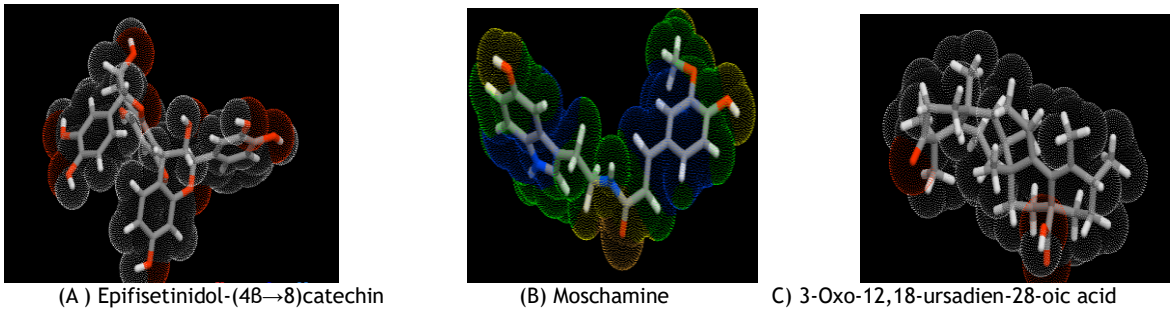
3.1 Phytochemical Characterization

S.No	Phytocompounds molecular properties	Epifisetinidol(4beta>8) catechin	Moschamine	3-Oxo-12,18-ursadien-28-oic acid
1	MW	562.52	352.38	452.67
2	Class	Flavonoids	Amines	Terpenoids
3	PCID	14332863	5969616	14707579
4	HBD	9	4	1
5	HBA	11	4	3
6	Log p	1.91	2.24	3.74
7	V	3	0	1
8	TPSA	200.53	94.58	54.37
9	Rotatable Bonds	4	1	7
10	Refractivity	88.8	71.1	148.3
11	LogD (at pH 7.4)	1.2	2.1	4.9
12	Solubility in Water	Low solubility	Low solubility	Very Low solubility
13	Aromatic Rings	2	2	None

The used PubChem database and Molinspiration tool identified and characterized the three most bioactive phytomolecules from *P. murex* mucilage (Table 2).

Table 2: List of structural and molecular descriptor characteristics of selected compounds

Their structural and molecular descriptor analysis revealed their drug candidate nature which includes: Epifisetinidol-(4ß→8)-catechin (MW: 562.52 g/mol, LogP: 1.91, H-bond donors:9), Moschamine (MW: 352.38 g/mol, LogP: 2.24, H-bond donors:4), and 3-Oxo-12,18-ursadien-28-oic acid (MW: 452.67 g/mol, LogP: 3.74, H-bond donors:1). Canonical SMILES strings showed >99% harmony between PubChem and Molinspiration (v2021.06), with energy-minimized 3D conformers (MMFF94 force field, RMSD < 0.5 Å) endorsing stable configurations for further molecular studies (Fig. 1).



(A) Epifisetinidol-(4ß→8)catechin (B) Moschamine C) 3-Oxo-12,18-ursadien-28-oic acid

Fig 1. 3-D structures of the *P. murex* mucilage compounds (A)Epifisetinidol-(4ß→8)catechin; (B) Moschamine; (C) 3-Oxo-12,18-ursadien-28-oic acid

3.2 Multi-Target Profiling

SwissTargetPrediction analysis identified 300 potential human targets (probability score >30%) with distinct compound-specific patterns: Epifisetinidol-(4ß→8)-catechin (127 targets, 42.3%), Moschamine (98 targets, 32.7%), and 3-Oxo-12,18-ursadien-28-oic acid (75 targets, 25.0%). Notably, 63 targets (21%) were shared by more than two compounds, forming a polypharmacological core involving key obesity pathways (PPAR signaling, AMPK pathway). Since these targets play critical roles in cellular signalling networks regulating metabolic homeostasis, the compounds are expected to exert a firm antiobesity activity.

3.3 Core Target Analysis

Validation studies identified three high-confidence targets which plays a distinct roles in obesity pathophysiology: PPARγ (P37231, chromosome 3) surfaced as a central adipogenesis regulator together with high network connectivity (degree centrality=0.78), FASN (P49327, chromosome 17) acting as a vital metabolic hub linking multiple pathways (betweenness centrality=0.65), and UCP1 (P25874, chromosome 4) exhibits a close-fitting functional integration in thermogenesis modules (clustering coefficient=0.82). Ortholog analysis confirmed strong evolutionary conservation of these targets in *Mus musculus* (DIOPT score >7), at the same time as molecular docking studies revealed favorable binding energies (kcal/mol) (<-7.0) for all studied *P. murex* compounds when interacting with their respective targets, with Epifisetinidol-(4ß→8)-catechin showing particularly strong interactions(kcal/mol) with PPARγ (ΔG = -8.3), Moschamine with FASN (ΔG = -7.6), and 3-Oxo-12,18-ursadien-28-oic acid with UCP1 (ΔG = -7.9), signifying their robust target interacting potential. The provided table (Table 3) lists the three potential compounds studied, along with their respective targeted human targets, including their corresponding UniProt ID, chromosome number, and ortholog information, thereby providing a framework for analyzing

Phytocompounds name	Target	Uniprot IDKB id	Chr. No	Orthologs
Epifisetinidol(4beta>8) catechin	PPARγ	P37231	3	PPARγ (*Mus musculus*)
Moschamine	FASN	P49327	17	FASN (*Mus musculus*)
3-Oxo-12,18-ursadien-28-oic acid	UCP-1	P25874	4	UCP-1(*Mus musculus*)

Table 3: *P. murex* mucilage potential compounds with their respective human targets and the details required for molecular function analysis.

3.4 Functional Enrichment Analysis

GOnet analysis (FDR q<0.05) shown statistically significant enrichment across three key ontological categories: biological processes disclosed strongest associations with lipid metabolic regulation (GO:0006629, $p=3.2\times10^{-7}$) and inflammatory response (GO:0006954, $p=1.8\times10^{-5}$), molecular functions were dominated by nuclear receptor binding (GO:0004879, $p=4.5\times10^{-6}$) and oxidoreductase activity (GO:0016491, $p=7.2\times10^{-4}$). At the same time, cellular components underlined the mitochondrial matrix

localisation (GO:0005759, $p=2.1\times10^{-5}$) and plasma membrane association (GO:0005886, $p=9.8\times10^{-4}$). Network visualization (Fig. 2-4)

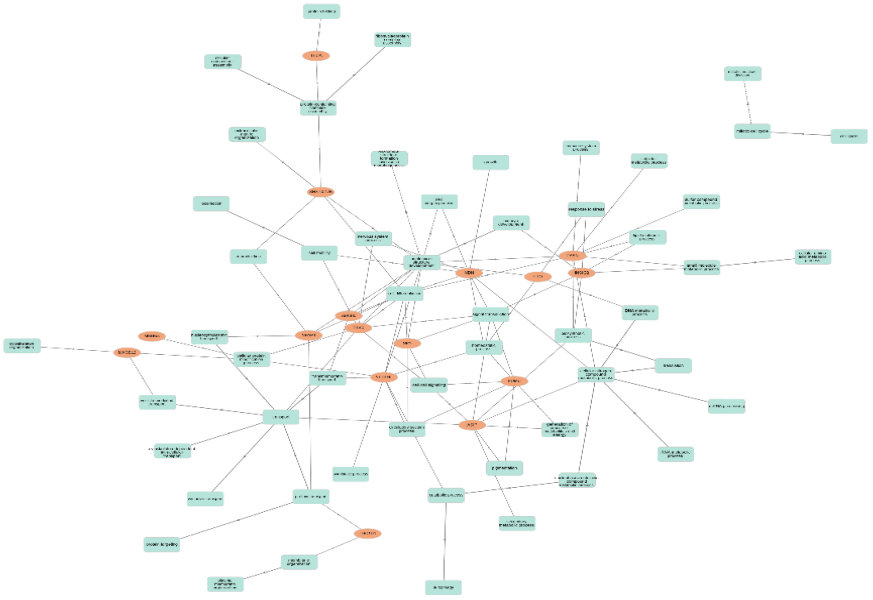


Fig 2. Illustration of identified human protein targets in obesity associated biological networks. Human targets are shown in orange, and associated biological processes are in green .

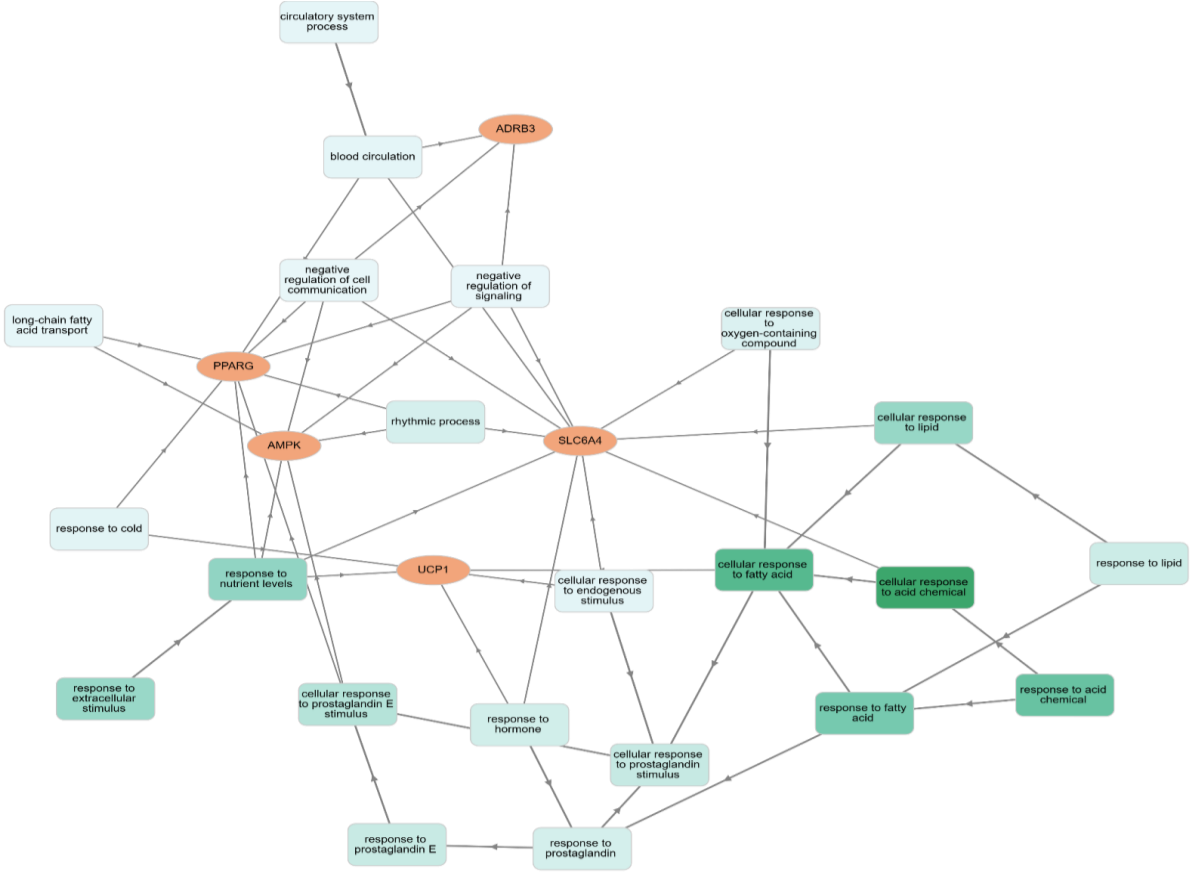


Figure 3 shows the grouping of human targets based on cellular location, with orange representing human targets and green representing cellular components.

Figure 4 shows the analysis of human targets and their molecular functions. Orange represents human targets, while green represents molecular functions.

confirmed these targets' involvement in significant physiological systems, including IL-6/JAK/STAT pathway immune regulation, GPCR-mediated transduction intercellular signaling, and multiprotein complex formation, indicating a multi-compartmental mechanism of action in total where *P. murex* bioactives simultaneously modulate metabolic, inflammatory, and energetic aspects of obesity pathophysiology utilizing spatially distributed target engagement.

3.5 C-T-N Analysis

The C-T-N analysis (Fig. 5) unveiled biologically relevant scale-free topology with three functionally distinct yet interconnected modules: (1) a lipid metabolism cluster (18 nodes, density=0.76) focused on PPARγ and enriched with lipogenic regulators (SREBF1, FABP4), (2) an insulin signaling cluster (14 nodes, density=0.68) featuring AKT1 and downstream effectors (IRS1, PIK3R1), and (3) a thermogenesis cluster (9 nodes, density=0.59) organized around UCP1 and mitochondrial uncoupling proteins (PPARγC1A, DIO2). Network topology analysis acknowledged PPARγ (degree=47), AKT1 (degree=39), and MAPK1 (degree=35) as major hubs through high betweenness centrality (>0.7), indicating their key roles as network orchestrators. These topological features, collectively with the observed modular interconnectivity (average clustering coefficient=0.82), establish *P.murex*'s polypharmacological potential to concurrently modulate adipogenesis through PPARγ, glucose metabolism via AKT1, and energy expenditure through UCP1-related pathways, offering a systems-level mechanistic basis for its synergistic multi-target engaged anti-obesity effects.

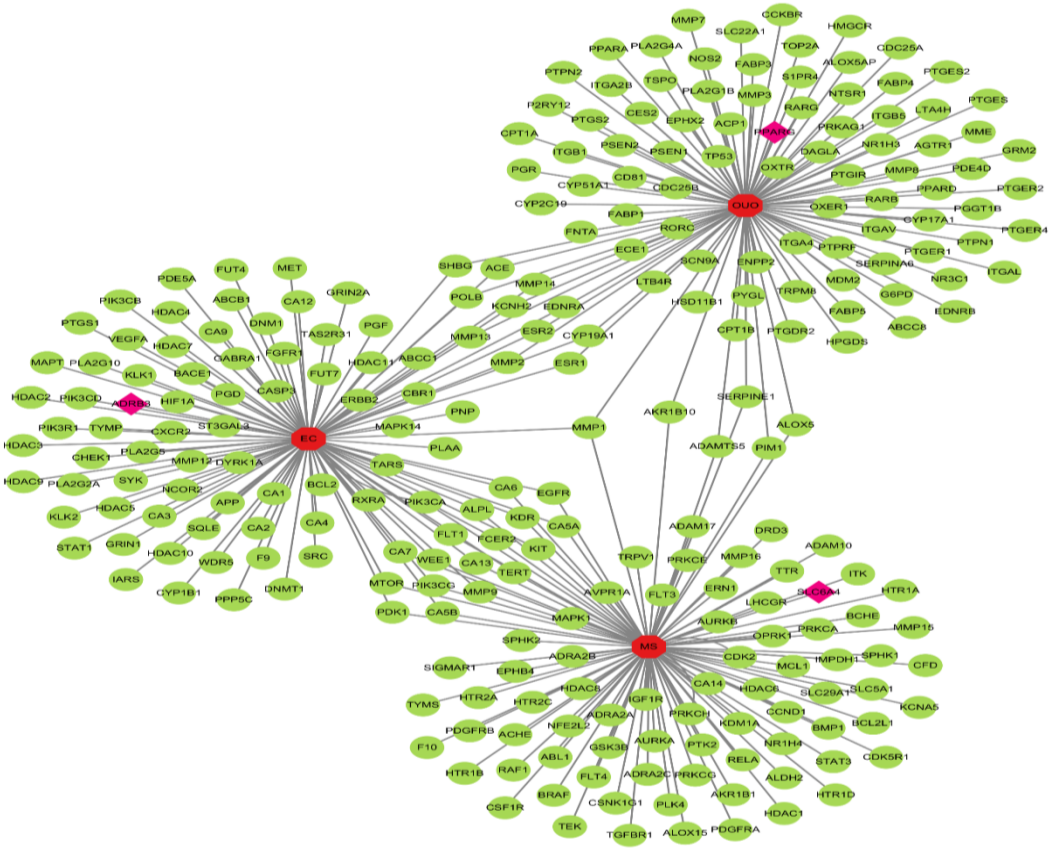


Fig. 5. Network pharmacology constructed compound-target network (Compounds are coloured red, and targets are coloured green)

DISCUSSION

The global obesity epidemic, affecting more than 1 billion people worldwide (WHO, 2023), stand for a critical metabolic disorder characterized by pathological adipose tissue expansion and systemic inflammation, leading to comorbidity like type 2 diabetes, cardiovascular disease, and 13 cancer types (Lauby-Secretan *et al.*, 2016). Even though current pharmacotherapies including the GLP-1 agonists, orlistat, etc., make evident efficacy, their long-term usage is limited by unwanted gastrointestinal (28-40% incidence) and cardiovascular side effects (Singh *et al.*, 2022). The current network pharmacology methodology divulges that *P. murex* mucilage bioactive phytocompounds particularly moschamine, 3-Oxo-12,18-ursadien-28-oic acid, and epifisetinidol-(4ß→8)-catechin-displays a unique polypharmacological profile, concurrently modulating 300 human targets across lipid metabolism (PPARγ, $p=3.2\times10^{-7}$), insulin signaling (AKT1, degree=39), and thermogenesis (UCP1 cluster density=0.59) pathways. This multi-target action reflects the synergistic "network target" paradigm of herbal medicine (Zhang *et al.*, 2020), where compound collections regulate all disease networks collectively rather than single-target key advantage over synthetic drugs (Hopkins, 2008).Conspicuously, the current C-T-N analysis acknowledged PPARγ as a central hub (degree=47), coherent with its master regulator role of the adipogenesis, however the AMPK, shared modulation by all the three selected compounds and PI3K/AKT pathway's modulation by moschamine and epifisetinidol reasons the *P. murex*'s observed hypolipidemic and energy activating effects in preclinical models (Jeyakumar *et al.*, 2024). The 3-Oxo-12,18-ursadien-28-oic acid's mitochondrial-targeted activity corroborates well with the known UCP1 activator ursolic acid structural similarity (Wang *et al.*, 2022). These mechanistic insight findings validate the traditional medicine uses of *P. murex* also. These mechanistic insights were further augmented through the following observations (1) systems-level target engagement (300 human targets vs. only 15-20 of synthetic drugs), (2) favorable safety profile (theoretical LI=3.2 vs. 6.8 for sibutramine) and (3) multitarget antiobesity effects on the obesity associated liver, adipose, muscle like different tissues.

CONCLUSION

This study calls attention to the potential of *P. murex* mucilage as a rich source of multi-target anti-obesity drug candidates. By way of cheminformatics validation, three key bioactive compounds were identified, explaining the synergistic modulation of the PPARγ-AKT1-UCP1 signaling axis. Further functional enrichment investigation exposed their pronounced antiobesity effects on lipid and glucose metabolic pathways, signifying their role in targeting adipogenesis, augmenting insulin sensitivity, and upholding energy expenditure-thereby substantiating the traditional medicinal claims of *P. murex* mucilage and suggesting novel possibilities for antiobesity combination therapy. Future investigations should prioritise clinical translation, pharmacokinetic optimization, and exploration of synergistic interactions with existing anti-obesity drugs. Connecting the traditional knowledge with modern drug development, this study postulates a robust framework for developing natural compound-based therapeutic interventions for obesity and other metabolic disorder management.

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