

**IN SILICO NETWORK PHARMACOLOGY INVESTIGATION OF
TYPHONIUM TRILOBATUM IN PROTEIN-ENERGY MALNUTRITION:
DECIPHERING BIOACTIVE COMPOUNDS, MOLECULAR TARGETS
AND SIGNALING PATHWAYS**

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ABSTRACT

Background: Protein Energy Malnutrition is a major global nutritional disorder characterized by impaired growth, metabolic dysfunction, immune suppression, oxidative stress, and progressive tissue wasting. Traditional ethnobotanical medicinal plants possessing nourishing and restorative properties may offer multitarget therapeutic potential in the management of PEM. Typhonium diversifolium has long been utilized in folklore medicine for its claimed nutritional and strengthening effects however, limited phytochemical documentation restricts systematic pharmacological investigation. Therefore, Typhonium trilobatum, a closely related species with better phytochemical representation, was selected for exploratory scientific validation of these traditional claims using a network pharmacology approach. **Aim:** The present study aimed to investigate the molecular mechanisms

underlying the ethnobotanical nutritional claims associated with *Typhonium trilobatum* against Protein Energy Malnutrition through integrative network pharmacology analysis.

Materials and Methods: Phytochemicals associated with *Typhonium trilobatum* were retrieved from the IMPPAT 2.0 Database and screened using SwissADME and MolSoft for pharmacokinetic evaluation and drug-likeness. Compound targets were predicted using SwissTargetPrediction, while disease-associated genes related to Protein Energy Malnutrition were retrieved from GeneCards and OMIM databases. Common targets were identified through Venn diagram analysis, followed by network construction using Cytoscape and hub gene analysis using the CytoHubba Plugin. Pathway enrichment analysis was performed using DAVID Bioinformatics Resources 2021. **Results:** A total of 9 phytochemicals were retrieved, among which 3 phytoconstituents satisfied the drug-likeness and ADME screening criteria. Target prediction yielded 278 targets, of which 241 unique targets remained after duplicate removal. Disease gene retrieval identified 248 PEM-associated genes, and comparative analysis revealed 15 overlapping targets. Network analysis highlighted the multitarget therapeutic nature of the selected phytochemicals, particularly thiamine, beta-sitosterol, and nicotinic acid. Hub gene analysis identified NOS2, TNF, CXCR3, MDM2, HCAR2, CA1, CA2, and F2 as significant regulatory targets. Pathway enrichment analysis revealed 41 enriched pathways, among which 20 pathways were directly linked to Protein Energy Malnutrition, including PI3K-Akt signaling, mTOR signaling, insulin resistance, HIF-1 signaling, adipocytokine signaling, and endocrine regulatory pathways. **Conclusion:** The present study provides preliminary scientific evidence supporting the traditional nutritional claims associated with *Typhonium trilobatum* in the management of Protein Energy Malnutrition. The identified phytoconstituents demonstrated multitarget interactions with inflammatory, metabolic, and nutritional regulatory pathways, suggesting promising therapeutic potential. The study also highlights the importance of scientifically validating extrapharmacopoeial (*Anukta Dravya*) medicinal plants through modern network pharmacology approaches.

INTRODUCTION

Protein Energy Malnutrition remains one of the most significant global public health concerns, particularly affecting children, pregnant women, and socioeconomically vulnerable populations.^[1] It is characterized by inadequate intake and utilization of proteins and calories, resulting in impaired growth, muscle wasting, immune dysfunction, micronutrient deficiencies, delayed wound healing, and increased susceptibility to infections.^[2]

The multifactorial pathophysiology of Protein Energy Malnutrition (PEM) involves disturbances in nutrient metabolism, oxidative stress, inflammatory mediators, hormonal imbalance, and impaired cellular repair mechanisms.^[3] Despite advances in nutritional supplementation and therapeutic interventions, PEM continues to contribute substantially to morbidity and mortality worldwide, especially in developing countries.^[4,5]

In Ayurveda, conditions resembling PEM can be correlated with states of *Karshya*, *Balakshaya*, *Dhatukshaya Vyadhis*, where depletion of *Rasa*, *Mamsa*, *Meda*, and subsequent impairment of *Ojas* occur due to inadequate nourishment and metabolic dysfunction.^[6] Classical Ayurvedic principles emphasize the restoration of *Dhatu Poshana*, enhancement of *Agni*, and strengthening of systemic vitality through nutrient-rich medicinal plants and dietary interventions.^[7,8] Several ethnobotanical drugs traditionally utilized by tribal and rural communities have been reported to possess nourishing, rejuvenating, and restorative properties that may support the management of malnutrition and wasting disorders.^[9,10]

Among such medicinal plants, *Typhonium diversifolium* has gained folkloric importance in certain Himalayan and indigenous regions due to its traditionally claimed nutritional and strengthening properties.^[11] The plant is reportedly consumed in local traditional practices for improving physical strength, nourishment, and general vitality.^[12] However, despite its ethnomedicinal significance, comprehensive phytochemical profiling and molecular pharmacological data regarding *Typhonium diversifolium* remain inadequately represented in currently available scientific databases, limiting systematic computational investigations.^[13]

Therefore, the present study utilized *Typhonium trilobatum* as a surrogate ethnobotanical candidate owing to its close taxonomic affiliation, structural similarity, and comparatively better phytochemical documentation.^[14] Species belonging to the same genus frequently exhibit similarities in secondary metabolite composition and biological activities, thereby supporting the exploratory utilization of *Typhonium trilobatum* for preliminary mechanistic validation of traditional nutritional claims associated with the genus.^[15] Furthermore, *Typhonium trilobatum* is considered an extrapharmacopoeial medicinal plant and may be categorized under *Anukta Dravya*, denoting medicinal substances that are not extensively described in classical Ayurvedic compendia but are recognized through regional folklore practices and empirical therapeutic utility.^[16,17]

Previous phytochemical investigations on *Typhonium trilobatum* have demonstrated the presence of diverse bioactive constituents including flavonoids, phenolic compounds, sterols, alkaloids, glycosides, and other secondary metabolites known to exhibit antioxidant, anti-inflammatory, immunomodulatory, metabolic regulatory, and cytoprotective activities.^[18] Such pharmacological properties may hold therapeutic relevance in the management of PEM, where chronic inflammation, oxidative stress, impaired protein synthesis, and metabolic dysregulation significantly contribute to disease progression.

Traditional herbal medicines often exert therapeutic effects through multi-target and multi-Pathway interactions rather than through a single molecular mechanism.^[19] In this context, network pharmacology has emerged as an advanced systems biology-based approach integrating pharmacology, bioinformatics, and computational biology to elucidate the complex interactions among phytochemicals, molecular targets, signaling pathways, and disease mechanisms.^[20] This holistic approach is particularly suitable for investigating ethnobotanical medicinal plants possessing multiple phytoconstituents acting synergistically on diverse biological networks.^[21]

Accordingly, the present study aimed to investigate the molecular mechanisms underlying the traditional nutritional claims associated with *Typhonium trilobatum* against Protein Energy Malnutrition using an integrative network pharmacology approach. By employing phytochemical screening, drug-likeness evaluation, ADME analysis, target prediction, disease-gene mapping, network construction, and hub gene identification, this study attempts to provide a scientific rationale for the ethnobotanical relevance of *Typhonium trilobatum* and establish a foundation for future experimental and clinical validation.

METHODS

Selection and Retrieval of Phytochemicals

In the present study, phytochemicals associated with *Typhonium trilobatum* were identified using the Indian Medicinal Plants, Phytochemistry and Therapeutics (IMPPAT) 2.0 Database.^[22] This database provides curated phytochemical information related to Indian medicinal plants based on experimentally reported literature and published scientific evidence. Since comprehensive phytochemical profiling data for *Typhonium diversifolium* were insufficiently represented in currently available databases, *Typhonium trilobatum* was selected as a surrogate ethnobotanical candidate owing to its close taxonomic and structural similarity.

Subsequently, each retrieved phytochemical compound was individually searched in the PubChem Database, an openly accessible chemical information repository maintained by the National Center for Biotechnology Information (NCBI), National Institutes of Health.^[23] From PubChem, the PubChem Compound ID (CID), molecular structure, and Canonical Simplified Molecular Input Line Entry System (SMILES) notation for each phytoconstituent were retrieved for further computational analysis.

Drug-Likeness Screening

The phytochemicals retrieved from the IMPPAT 2.0 Database were subjected to drug-likeness evaluation using SwissADME and the MolSoft Online Tool, which predict drug-like characteristics and pharmacokinetic behavior based on molecular structure and physicochemical properties.^[24,25] The canonical Simplified Molecular Input Line Entry System (SMILES) notation retrieved from the PubChem Database was used as input for analysis. Each phytochemical was evaluated for molecular properties including molecular weight, lipophilicity, hydrogen bond donor and acceptor count, and overall drug-likeness score. Compounds with favorable drug-likeness characteristics, oral bioavailability, and acceptable pharmacokinetic profiles were considered suitable for further investigation, following established criteria commonly employed in network pharmacology-based phytochemical screening studies. The shortlisted phytoconstituents were subsequently selected for ADME profiling and target prediction analysis.

Absorption, Distribution, Metabolism, and Excretion Profiling

The phytochemicals that successfully passed the preliminary drug-likeness screening were further subjected to pharmacokinetic evaluation using SwissADME.^[26] The Canonical Simplified Molecular Input Line Entry System (SMILES) notation retrieved from the PubChem Database was used as input for the analysis.

The SwissADME platform was employed to predict important pharmacokinetic parameters including gastrointestinal (GI) absorption, blood–brain barrier permeability, P-glycoprotein substrate characteristics, bioavailability, and cytochrome P450 enzyme interactions. Furthermore, each phytochemical was evaluated according to Lipinski's Rule of Five, which assesses the oral drug-likeness of compounds based on molecular weight, lipophilicity (LogP), hydrogen bond donors, and hydrogen bond acceptors.^[27] Phytoconstituents showing favorable ADME characteristics with zero or a maximum of one violation of Lipinski's

criteria were considered suitable for further target prediction and network pharmacology analysis.

Compound Target Prediction

The potential biological targets of the shortlisted phytochemicals were predicted using the SwissTargetPrediction Online Tool.^[28] The Canonical Simplified Molecular Input Line Entry System (SMILES) notation for each selected phytochemical, previously retrieved from the PubChem Database, was used as input, and the target organism was set as *Homo sapiens*. The platform generated a list of predicted protein targets along with their associated probability scores based on chemical similarity and known ligand-target interactions.^[29]

A total of 278 predicted targets were initially obtained from all shortlisted phytoconstituents. After removal of duplicate entries, 241 unique targets remained and were considered for further analysis. These filtered targets were subsequently utilized for compound–target network construction and downstream biological interpretation through network pharmacology analysis.

Disease-Associated Gene Retrieval

To identify genes associated with Protein Energy Malnutrition, a comprehensive search was performed using two biomedical databases: GeneCards and OMIM (Online Mendelian Inheritance in Man).^[30,31] The keywords “Protein Energy Malnutrition” and “Malnutrition” were used as search terms in both databases to retrieve disease-associated genes relevant to the pathophysiology of PEM. The obtained genes from both databases were compiled, merged, and duplicate entries were removed to generate a unified disease-associated gene dataset. To improve the reliability and biological relevance of the analysis, genes with higher relevance scores were prioritized for downstream analysis, including overlapping target identification, compound–target–disease network construction, and hub gene analysis.

Identification of Common Target Genes via Venn Diagram

To identify the shared genes between the predicted targets of the selected phytochemicals and the genes associated with Protein Energy Malnutrition, a Venn diagram analysis was performed using an online Venn analysis platform.^[32] This comparative analysis enabled the identification of overlapping genes representing potential therapeutic targets through which the selected phytoconstituents of *Typhonium trilobatum* may exert beneficial effects against Protein Energy Malnutrition. The identified common targets were considered biologically

significant and were subsequently utilized for further network pharmacology analysis, including compound–target–disease network construction, hub gene identification, and pathway enrichment analysis.

Network Construction and Hub Gene Identification

To visualize the interactions between the selected phytochemicals and their common target genes associated with Protein Energy Malnutrition, a compound–target network was constructed using Cytoscape, an open-source software platform widely used for complex network visualization and bioinformatics analysis.^[33] The overlapping genes identified through Venn diagram analysis were imported into Cytoscape to establish the interaction network between phytoconstituents and disease-associated targets.

To identify the most significant genes within the constructed network, the CytoHubba Plugin was employed. CytoHubba utilizes multiple topological algorithms to determine hub genes based on their connectivity and biological importance within the network. Genes exhibiting higher degrees of interaction and centrality were considered potential hub genes and may play crucial roles in the therapeutic mechanisms of the selected phytochemicals against Protein Energy Malnutrition. The top-ranked hub genes identified through this analysis were selected for further biological interpretation and pathway analysis.

RESULTS

Phytochemical Retrieval and Drug-Likeness Screening

A total of 9 phytochemicals associated with *Typhonium trilobatum* were retrieved from the IMPPAT 2.0 Database. These phytoconstituents were subjected to drug-likeness evaluation using SwissADME and the MolSoft Online Tool to assess their pharmacokinetic and molecular properties. Following drug-likeness screening and pharmacokinetic evaluation, 3 phytochemicals satisfied the required screening criteria and demonstrated favorable drug-like characteristics. These shortlisted phytoconstituents were subsequently selected for further ADME profiling, target prediction, and network pharmacology analysis.

Absorption, Distribution, Metabolism, and Excretion Profiling

The three shortlisted phytochemicals underwent ADME analysis using SwissADME to evaluate their pharmacokinetic and drug-likeness properties. The analysis included assessment of gastrointestinal absorption, bioavailability, Lipinski's Rule of Five compliance, and other important pharmacokinetic parameters associated with oral therapeutic suitability.

All three phytochemicals demonstrated favorable ADME profiles with acceptable pharmacokinetic characteristics, indicating good oral bioavailability and drug-like properties suitable for further network pharmacology investigation.

Table 1: Pharmacokinetic evaluation.

Sr.No	Phytochemical	Drug Likeliness	Molecular weight	Bioavailability
A.	Thiamine	0.29	265.35 g/mol	0.55
B.	Nicotinic acid	0.3	123.11 g/mol	0.85
C.	beta-Sitosterol	0.78	414.71 g/mol	0.55

Target Prediction

Using the SwissTargetPrediction Tool, a total of 278 potential compound targets were predicted for the three shortlisted phytochemicals of *Typhonium trilobatum*. The prediction was performed using Canonical SMILES as input with the target organism set as *Homo sapiens*. Following target compilation, duplicate entries were removed to improve data accuracy and reliability. After filtration, 241 unique targets remained and were considered for subsequent network pharmacology analysis, including overlapping target identification, compound–target network construction, and hub gene analysis.

Disease Gene Retrieval

A comprehensive search was performed using the GeneCards Database and OMIM Database to identify genes associated with Protein Energy Malnutrition. The keywords “Protein Energy Malnutrition” and “Malnutrition” were used as search terms in both databases to retrieve disease-associated genes relevant to PEM pathology.

A total of 248 genes associated with Protein Energy Malnutrition were identified after compilation and removal of duplicate entries. These genes represent potential molecular targets involved in nutritional deficiency, metabolic dysregulation, immune impairment, and tissue wasting associated with PEM. The final consensus set of disease-associated genes was subsequently utilized for downstream analyses including overlapping target identification, compound–target–disease network construction, and hub gene analysis.

Venn Diagram Analysis

Comparative analysis using a Venn diagram tool revealed 15 common genes shared between the predicted targets of the selected phytochemicals and the genes associated with Protein Energy Malnutrition. These overlapping genes represent potential therapeutic targets through

which the phytoconstituents of *Typhonium trilobatum* may exert beneficial effects against Protein Energy Malnutrition. The identified common targets were considered biologically significant and were subsequently utilized for compound–target–disease network construction, hub gene identification, and further pathway enrichment analysis.

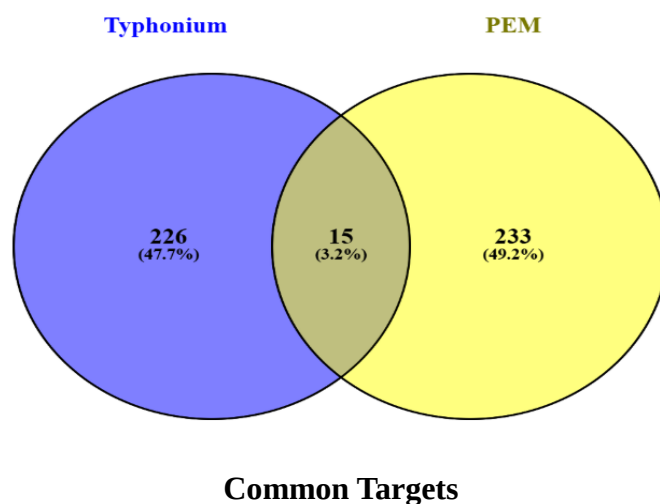
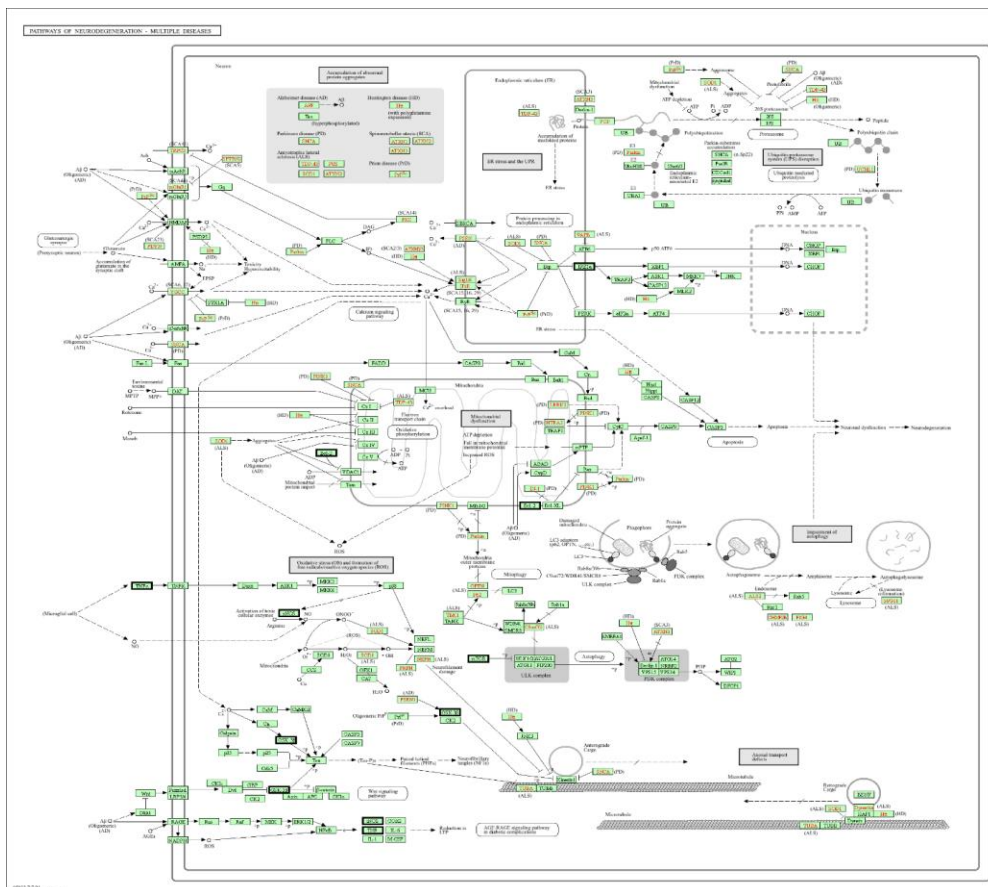
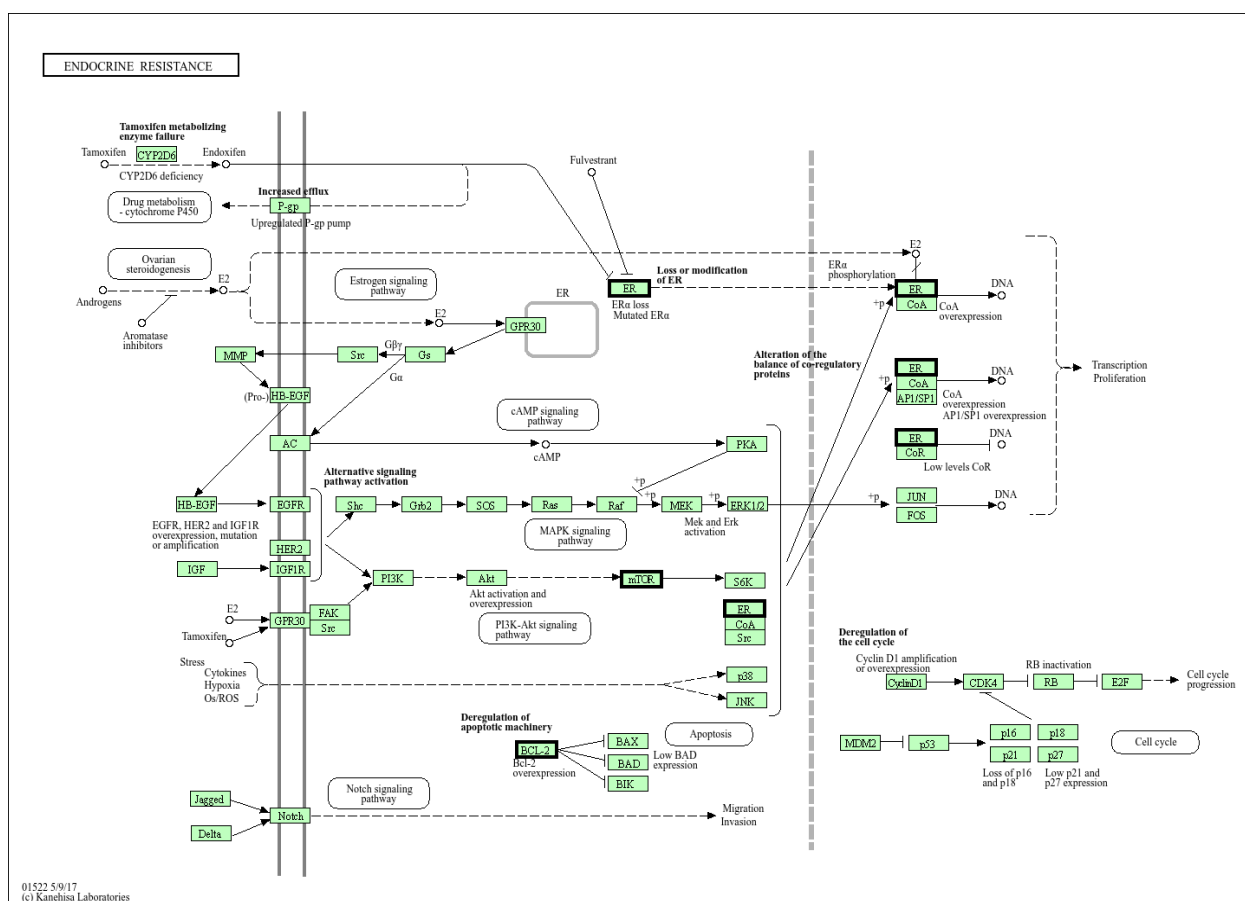


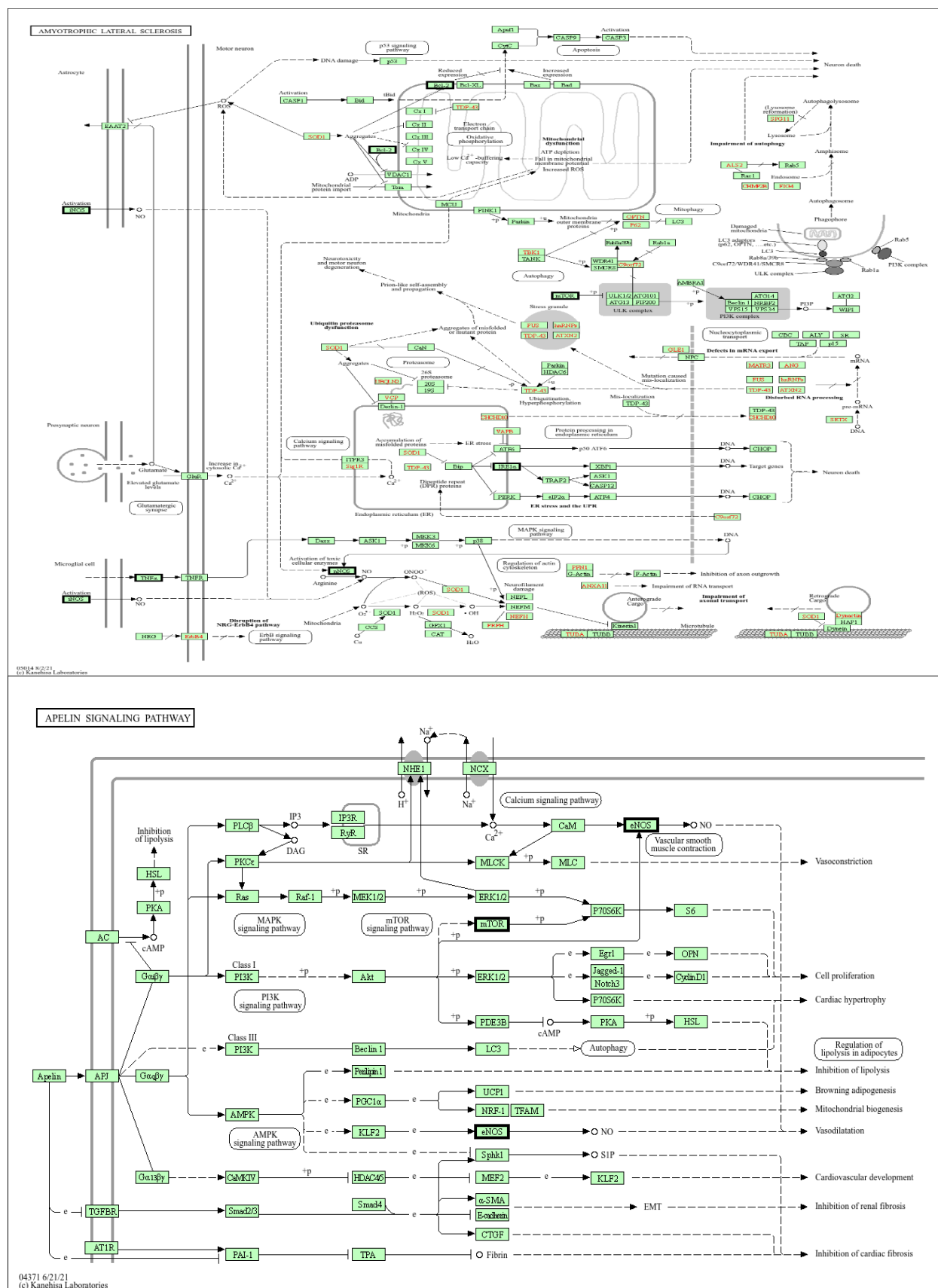
Figure 1: Venn diagram.

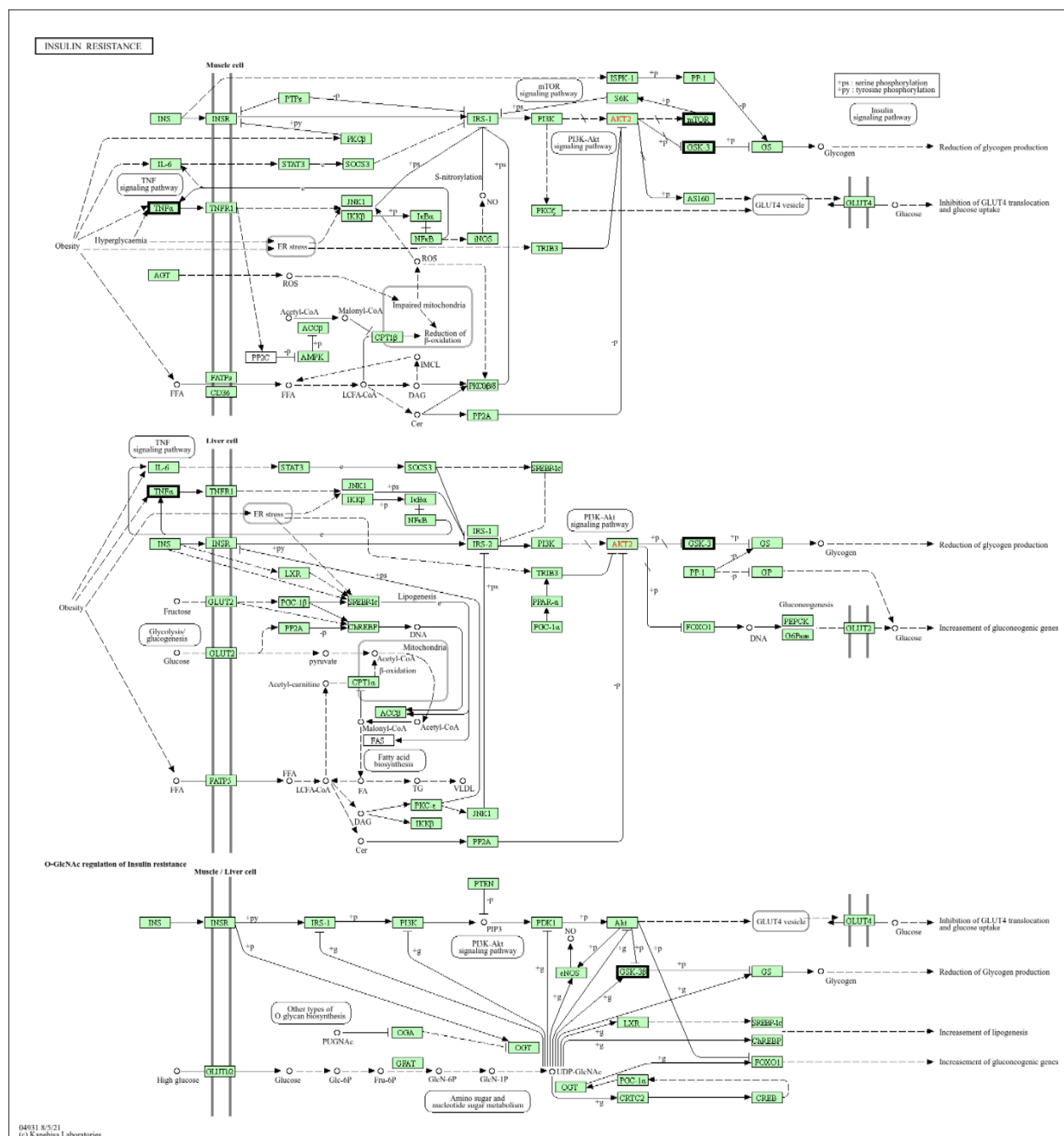
Pathway Enrichment Analysis

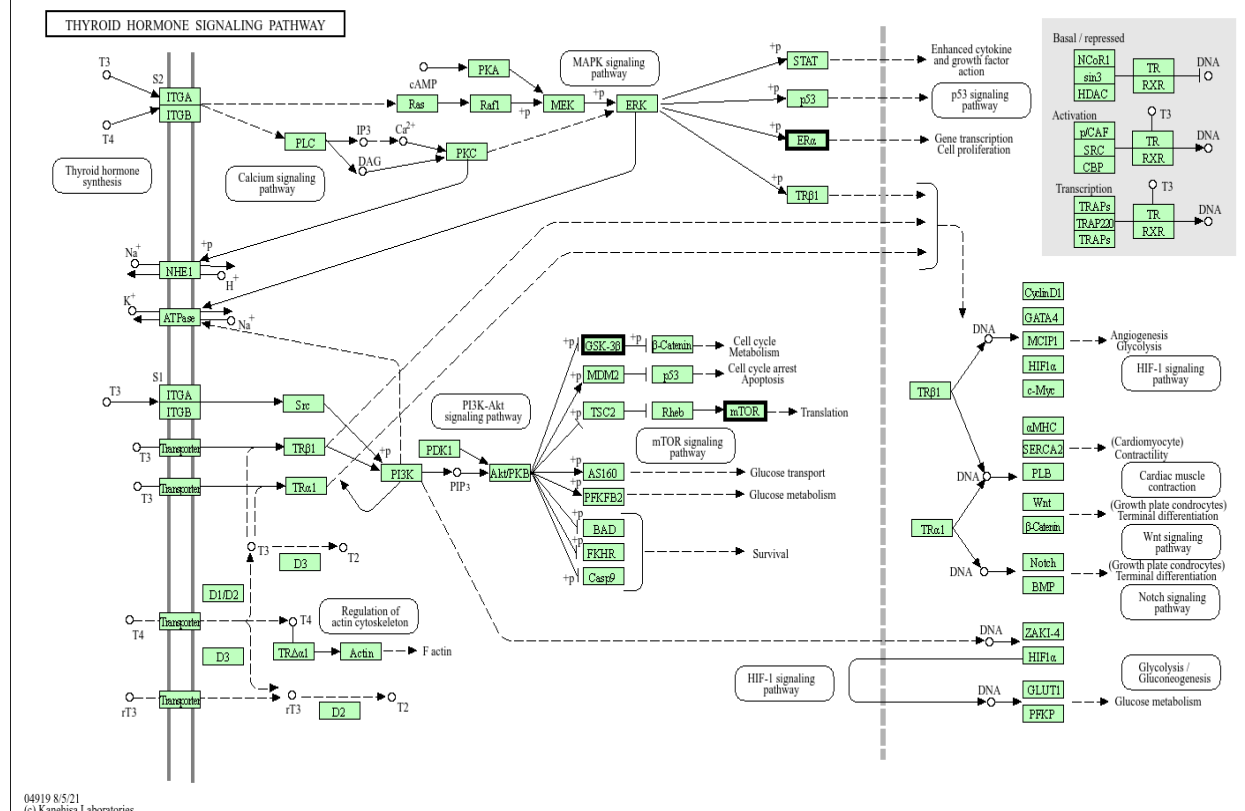
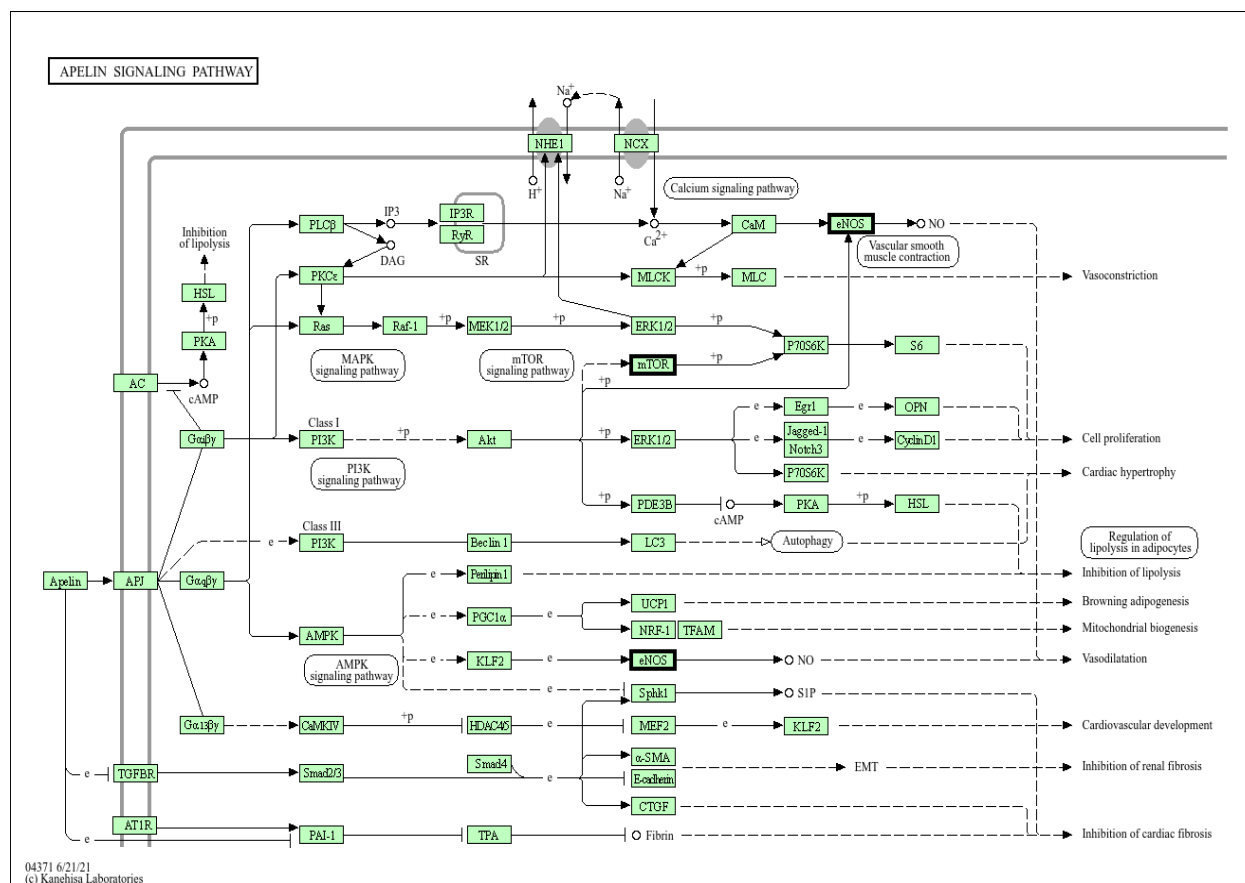


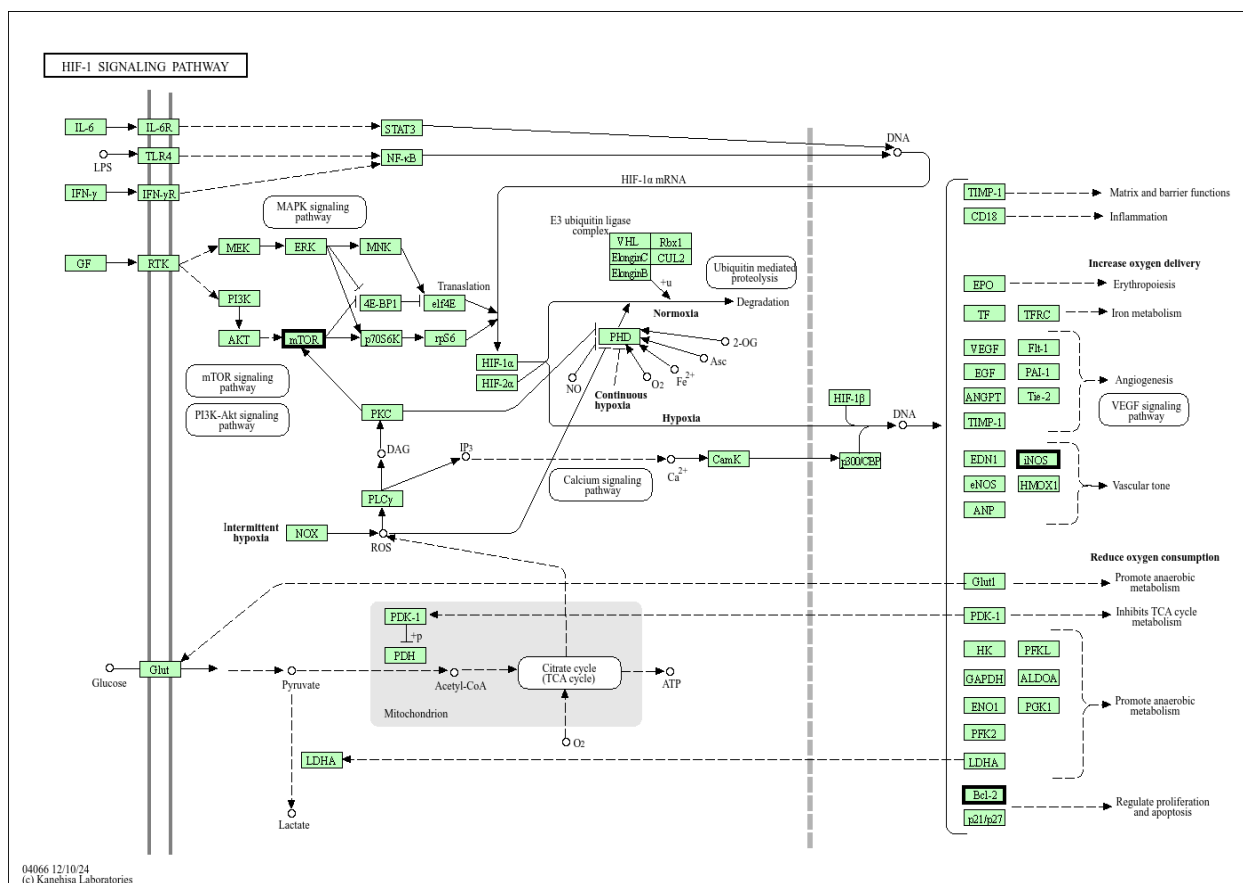
Pathway enrichment analysis was performed using the DAVID Bioinformatics Resources 2021 to identify the major biological pathways associated with the common target genes linked to *Typhonium trilobatum* and Protein Energy Malnutrition. The analysis was conducted to explore the biological significance and molecular mechanisms underlying the therapeutic potential of the selected phytoconstituents. A total of 41 enriched pathways were identified from the common target genes, among which 20 pathways were found to be directly associated with the pathophysiology and therapeutic modulation of Protein Energy Malnutrition. These pathways were mainly related to nutrient metabolism, inflammatory signaling, oxidative stress response, immune regulation, cellular survival, and metabolic adaptation, highlighting the multitarget and multipathway therapeutic potential of the selected phytochemicals.











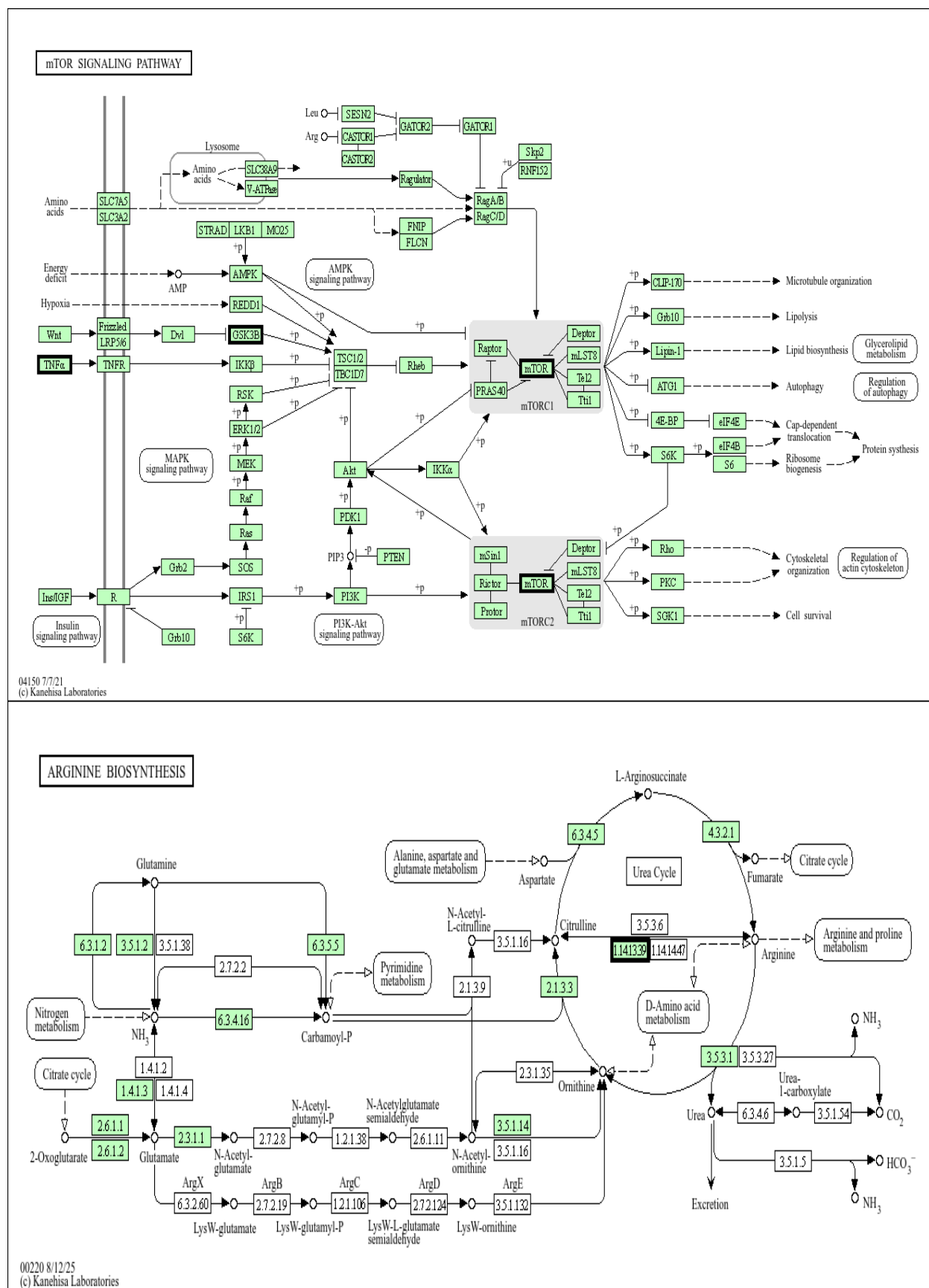


Figure- 2: Pathways Analysis.

Table 2: Pathways analysis.

Sr.No	Pathways
A.	Pathways of neurodegeneration - multiple diseases
B.	Amyotrophic lateral sclerosis
C.	Endocrine resistance
D.	Insulin resistance
E.	HIF-1 signaling pathway
F.	Thyroid hormone signaling pathway
G.	Apelin signaling pathway
H.	mTOR signaling pathway
I.	Arginine biosynthesis
J.	Arginine and proline metabolism
K.	Hedgehog signaling pathway
L.	PI3K-Akt signaling pathway
M.	Adipocytokine signaling pathway
N.	Prolactin signaling pathway
O.	ErbB signaling pathway

Network Analysis

The interaction network was constructed using Cytoscape to visualize the molecular interactions among *Typhonium trilobatum*, its bioactive phytoconstituents, and the associated target genes involved in Protein Energy Malnutrition. The constructed network highlighted the systemic interconnectivity and multitargeted therapeutic nature of the selected phytochemicals, demonstrating how a single ethnobotanical medicinal plant may modulate multiple molecular targets through diverse bioactive compounds.

Several genes were found to be interconnected with both the phytoconstituents and Protein Energy Malnutrition-associated targets, indicating shared molecular interactions between the medicinal plant and disease pathology. This network architecture supports a multitarget therapeutic approach, suggesting that the phytochemicals of *Typhonium trilobatum* may simultaneously regulate multiple biological pathways associated with nutrient metabolism, immune response, oxidative stress, and metabolic dysfunction.

The edges within the network represent direct or predicted interactions between plant-derived phytoconstituents and disease-associated proteins. The overall interaction pattern reflects the holistic and multitarget therapeutic concept underlying traditional medicinal systems and supports the polypharmacological nature of ethnobotanical interventions.

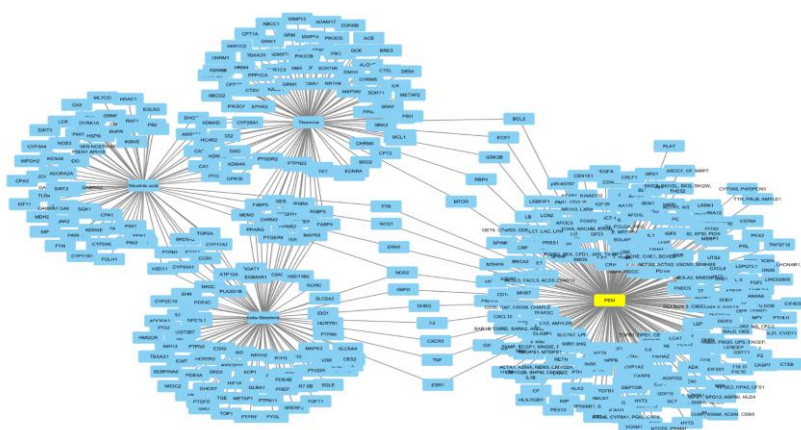


Figure 3: Network analysis.

Multi-Algorithm Hub Gene Ranking

Although degree-based connectivity is an important parameter in network analysis, the utilization of multiple topological algorithms provides a more reliable and consensus-oriented identification of the most influential hub genes within the interaction network. Therefore, the constructed compound–target–disease network was analyzed using the CytoHubba Plugin integrated within Cytoscape.

The network was evaluated using four major topological algorithms:

- **Degree:** Identifies nodes based on the number of direct interactions and overall connectivity within the network.
- **Maximal Clique Centrality (MCC):** Detects nodes participating in highly interconnected clusters and is considered one of the most effective methods for identifying essential biological targets.
- **Edge Percolated Component (EPC):** Measures node significance according to its contribution to network integrity and edge connectivity.
- **Closeness Centrality:** Ranks nodes according to their average shortest path distance to other nodes, indicating their potential ability to influence the overall network efficiently.

Table -5: Top 50 in network ranked by MCC method.

Rank	Name	Score
1	PEM	248
2	Thiamine	101
2	beta-Sitosterol	101

4	Nicotinic acid	77
5	Typhonium diversifloium	3
5	NOS2	3
7	CXCR3	2
7	F2	2
7	TNF	2
7	CA2	2
7	CA1	2
7	HCAR2	2
7	MDM2	2
7	PPARG	2
7	PPARA	2
7	PPARD	2
7	GPR35	2
7	PTGER1	2
7	RBP4	2
7	BCL2	2
7	KDM4C	2
7	MAPK8	2
7	FABP4	2
7	CHRM2	2
7	AKR1B1	2
7	PTGS2	2
7	PTGS1	2
7	GSK3B	2
7	TERT	2
7	DAO	2
7	KDM4D	2
7	PTGER4	2
7	DHODH	2
7	PTGES	2
7	PTGER2	2
7	KDM4A	2
7	ECE1	2
7	MTOR	2
7	FABP3	2
7	FABP5	2
7	PTPN1	2
7	CYP19A1	2
7	ERN1	2
7	NOS1	2
7	CYP17A1	2
7	TOP2A	2
7	HSD11B1	2
7	SRD5A2	2
7	TTR	2
7	CYP51A1	2

The top-ranked hub genes identified through these algorithms are presented in Figure 4. Consensus analysis across the algorithms highlighted NOS2, TNF, CXCR3, MDM2, HCAR2, CA1, CA2, and F2 as important regulatory targets potentially involved in the therapeutic effects of Typhonium trilobatum against Protein Energy Malnutrition.

Among the phytoconstituents, thiamine, beta-sitosterol, and nicotinic acid demonstrated prominent interactions with multiple disease-associated targets, suggesting their possible multitarget pharmacological role in the modulation of metabolic dysfunction, inflammation, oxidative stress, and nutritional imbalance associated with Protein Energy Malnutrition.

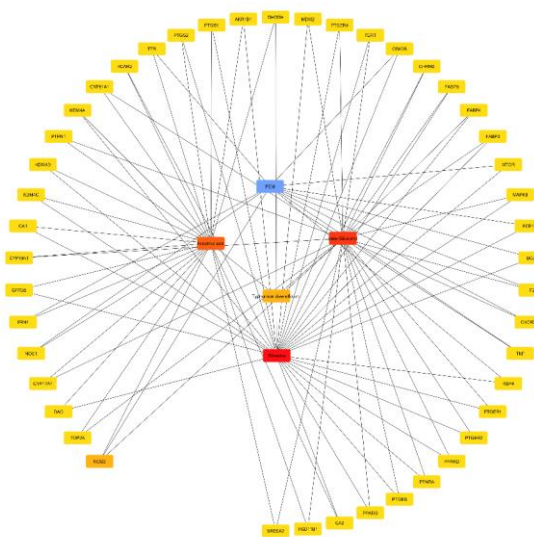


Figure- 4: The top-ranked hub genes.

DISCUSSION

The present study employed an integrative network pharmacology approach to scientifically explore the ethnobotanical and folklore nutritional claims associated with *Typhonium trilobatum* in the management of Protein Energy Malnutrition. Although the traditional nutritional claim is predominantly linked with *Typhonium diversifolium*, insufficient phytochemical representation of the species in currently available pharmacological databases necessitated the utilization of *Typhonium trilobatum* as a surrogate ethnobotanical candidate. Due to their close taxonomic affinity and structural resemblance, this approach provided a rational exploratory platform for mechanistic validation of traditional knowledge systems.

Protein Energy Malnutrition is a multifactorial metabolic disorder characterized not only by nutritional deficiency but also by chronic inflammation, oxidative stress, endocrine

dysregulation, impaired immune function, altered protein metabolism, and progressive tissue wasting. Conventional nutritional supplementation strategies primarily focus on caloric restoration; however, increasing evidence suggests that effective management of PEM also requires modulation of inflammatory and metabolic signaling pathways. In this context, medicinal plants possessing multitarget pharmacological actions may offer broader therapeutic advantages.

The present investigation identified nine phytochemicals from the IMPPAT database, among which thiamine, beta-sitosterol, and nicotinic acid demonstrated favorable drug-likeness and pharmacokinetic characteristics. These compounds satisfied ADME screening criteria and exhibited acceptable oral bioavailability, suggesting their suitability for systemic therapeutic activity. Importantly, all three phytoconstituents are biologically relevant to nutritional restoration and metabolic regulation. Thiamine plays a crucial role in carbohydrate metabolism and mitochondrial energy production, nicotinic acid participates in cellular redox reactions and energy homeostasis, whereas beta-sitosterol possesses anti-inflammatory, antioxidant, and immunomodulatory activities. Their simultaneous presence within the network indicates that the therapeutic potential of *Typhonium trilobatum* may not depend on a single compound but rather on synergistic multitarget interactions.

Target prediction analysis yielded 241 unique molecular targets, highlighting the broad pharmacological spectrum of the selected phytoconstituents. Comparative analysis further identified 15 overlapping targets between compound-associated proteins and PEM-related genes, indicating significant biological intersections between the phytochemicals and disease pathology. These shared targets suggest that the selected compounds may influence multiple pathological mechanisms simultaneously, including inflammation, metabolic imbalance, oxidative stress, nutrient utilization, and immune dysregulation. Such multitarget interactions align strongly with the systems-based therapeutic principles of traditional medicine and reinforce the concept of network pharmacology in ethnobotanical drug discovery.

Pathway enrichment analysis revealed 41 enriched pathways, among which 20 pathways were directly associated with the pathophysiology of Protein Energy Malnutrition. Particularly significant pathways included insulin resistance, HIF-1 signaling, PI3K-Akt signaling, mTOR signaling, adipocytokine signaling, arginine biosynthesis, and endocrine regulatory pathways. These pathways are critically involved in cellular growth, nutrient sensing, protein synthesis, metabolic adaptation, mitochondrial function, and inflammatory

regulation. The involvement of the PI3K-Akt and mTOR signaling pathways is especially noteworthy because these pathways regulate anabolic metabolism, muscle protein synthesis, and cellular survival, all of which are profoundly impaired in PEM. Similarly, modulation of insulin resistance and adipocytokine signaling may contribute toward improved nutrient utilization and metabolic recovery.

The identification of NOS2, TNF, CXCR3, MDM2, HCAR2, CA1, CA2, and F2 as major hub genes further strengthens the mechanistic significance of the study. TNF and NOS2 are well-recognized mediators of chronic inflammation and oxidative stress, both of which contribute substantially to muscle wasting and metabolic deterioration during malnutrition. Downregulation or modulation of these inflammatory mediators may therefore help attenuate tissue damage and systemic catabolism. CXCR3 is associated with immune cell migration and inflammatory signaling, suggesting a possible immunomodulatory role of the phytoconstituents. HCAR2 and MDM2 are involved in metabolic regulation, cellular stress responses, and energy homeostasis, while CA1 and CA2 participate in acid-base regulation and cellular metabolism. Collectively, these hub genes indicate that *Typhonium trilobatum* may exert therapeutic effects through coordinated regulation of inflammatory, metabolic, and adaptive stress-response pathways.

The constructed compound–target–disease interaction network further demonstrated the polypharmacological nature of the selected phytoconstituents. Unlike conventional single-target therapeutics, medicinal plants often function through simultaneous modulation of multiple interconnected biological pathways. This network-based therapeutic behavior reflects the holistic pharmacodynamic principles traditionally described in ethnomedicinal systems and supports the rationale behind folklore utilization of *Typhonium* species as nourishing and restorative agents.

From an Ayurvedic perspective, the observed molecular interactions may be interpreted in relation to *Brimhana*, *Balya*, and *Rasayana* actions, which promote tissue nourishment, metabolic strengthening, and restoration of vitality. The modulation of pathways associated with nutrient metabolism, immune function, and anabolic signaling provides a modern scientific correlation to these traditional therapeutic concepts. Furthermore, the classification of *Typhonium trilobatum* as an ectrpharmacopoeial or *Anukta Dravya* highlights the importance of documenting and scientifically validating regionally utilized medicinal plants that remain underexplored in classical literature.

Despite these promising findings, the present study possesses certain limitations. The investigation was entirely computational and based on predictive bioinformatics tools; therefore, the identified interactions require further validation through *in vitro*, *in vivo*, and clinical studies. Additionally, phytochemical data from *Typhonium trilobatum* were utilized as a surrogate model due to insufficient database representation of *Typhonium diversifolium*. Future phytochemical profiling and experimental evaluation of *Typhonium diversifolium* are therefore essential to establish species-specific therapeutic mechanisms and translational relevance.

Overall, the findings of the present study provide preliminary scientific evidence supporting the traditional nutritional claims associated with *Typhonium* species. The multitarget interactions of thiamine, beta-sitosterol, and nicotinic acid with key inflammatory and metabolic pathways suggest that *Typhonium trilobatum* possesses promising therapeutic potential in the management of Protein Energy Malnutrition. These results establish a scientific foundation for future pharmacological investigations and support the growing importance of integrating ethnobotanical knowledge with modern systems pharmacology approaches.

CONCLUSION

The present study provides preliminary scientific evidence supporting the traditional nutritional claims associated with *Typhonium trilobatum* in the management of Protein Energy Malnutrition. Through an integrative network pharmacology approach, key phytoconstituents including thiamine, beta-sitosterol, and nicotinic acid were identified as potential multitarget bioactive compounds involved in the modulation of inflammatory, metabolic, and nutritional pathways. The identification of significant hub genes and enriched signaling pathways further highlighted the possible therapeutic relevance of *Typhonium trilobatum* in restoring metabolic balance and nutritional homeostasis. Overall, the findings scientifically validate the ethnobotanical importance of this extrapharmacopoeial (*Anukta Dravya*) medicinal plant and provide a strong foundation for future experimental and clinical investigations.

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