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Network Ethnopharmacology: Unraveling Multitargeted Herbs and Formulations Along with Network Pharmacology of Ashwagandha and Trikatu

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Abstract

In Ayurveda, ancient science of well-being various herbs (Dravya) and formulations (Yoga) are mentioned to cure multiple diseases (Vyadhi). In Dravya Guna Shastra, the branch of Ayurveda, various fundamental principles (Siddhanta) are mentioned according to which all herbs and formulations target different systems of the body. However, validation of the claim by the Ayurvedic herbs or formulations always remains a challenge. Network pharmacology is a promising tool for overcoming this challenge. Network pharmacology is the approach that looks at how everything works together i.e. it makes us understand how different medicines, diseases, and various systems of our body are connected. It is the study of the complex network of drug action on various biological pathways and targets. This unique approach is similar to Ayurveda fundamentals that focus on the interaction between multiple components within the body while doing treatment by use of herbs and various herbal formulations. In this research paper integration of Ayurvedic knowledge with network pharmacology is mapped which helps in the future for drug discovery and scientific validation for Ayurvedic treatment strategies which ultimately contribute to the advancement of Ayurveda. Along with this network pharmacology of Ashwgandha and Trikatu by current research, active ingredients, related techniques/ tools/ databases, are also mentioned which helps the researcher to understand the phenomena of discovering the novel compounds and explore the full biological potential of Ayurvedic herbs and formulations using the network pharmacology.

Keywords

Network pharmacology, Ethnopharmacology, Network mapping, Herbs, Ayurvedic formulations, Drug discovery, Active ingredients.

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1. Introduction

1.1. Overview of Network Pharmacology

1.1.1. What is Network Pharmacology

Network pharmacology is a research field based on systems biology, genomics, proteomics, and other disciplines, which is a method to discover new drug targets and molecular mechanisms by combining computational analysis with in vivo and in vitro experiments and integrating a large amount of information [1].

1.1.2. Need for Network Pharmacology

Today one drug, one target, one approach that was followed for the last several decades is facing many challenges, of efficacy, sustainability, and safety. To overcome this challenge specific bullet-based drug discovery needed to be shifted towards multi-targeted drug discovery and for this network pharmacology comes into existence.

1.1.3. Existence of Pharmacology

In the first decade of the 21st century several biological networks under network biology were put forward that use literature mining and computational methods to understand diseases phenotype and genotype. As a result of this LMMA (literature mining and microarray analysis) was purposed to keep researchers up to date with large-scale datasets that are useful in making experimental designs and specific biological networks [2].

Andrew L Hopkins observed that network biology and Poly pharmacology can illuminate the understanding of drug action. He introduced the term Network pharmacology. Network pharmacology helps us to think beyond classic lock and key concepts as there can be multiple keys for a single lock and a single key can also fit in multiple locks means a target might connect with different types of ligands and a single ligand can interact with multiple targets. This concept is Poly pharmacology. The integration of network biology and poly-pharmacology was done which helps in tackling two major problems of drug discovery i.e. safety and efficacy. This integration is Network Pharmacology which is the next paradigm in drug discovery.

1.1.4. Contents of Network Pharmacology

Based on a regression model network pharmacology is a computational framework that comprises:

- Human protein-protein interaction
- Diseases phenotype similarities
- Gene phenotype association
- A network-based gene clustering

1.1.4.1. Tools Used

CIPHER (Correlating protein Interaction network and Phenotype network to predict disease genes) is used to discover the disease genes [2].

1.1.4.2. The Method Used

CIPHER-HIT, a Hitting-Time-based method is used to measure closeness between two nodes of a heterogeneous network globally [3].

1.2. Network Pharmacology in Ayurveda

As Ayurvedic herbs have been economically designed and synthesized by nature for the benefit of evolution, Ayurveda is gaining importance in the chemical space of drug discovery. Firstly an Oracle database and Internet technology are used in the field of Ayurveda to promote scientific research in Ayurvedic medicine. After this various databases are created that help to cover the bridge between Ayurveda medicines and modern molecular biology. When these databases are made this gives the idea to researchers to use network pharmacology to understand the mechanism of Ayurvedic herbs and formulations.

So, when network pharmacology is used to understand Ayurvedic herbs and formulation mechanisms and new drug discovery in the field of Ayurveda we can say it is Network ethnopharmacology [4].

1.3. How Network ethnopharmacology is used in Ayurveda

Network ethnopharmacology is used to understand the multifaceted interaction of herbs and various formulations with biological systems. In this mapping of a complex network of bioactive compounds present in herbs and their targets are done which helps to understand their mechanism of action.

2. Materials and Methods

All material was collected through Samhita, Nighantu, Recent textbooks of Ayurveda and pharmacology, and various online databases.

2.1. Choose the drug/formulation

With the help of various Ayurvedic classical literatures, first choose the drug/formulation whose network construction has to be done.

Detailed Ayurvedic study of a particular Herb and its formulation (each ingredient) should be done to understand its Dosha karma, its Agraya Karma (main action), and Karma on different parts of the body.

2.2. Different Database to be used to collect the knowledge of drug/formulation

- Information regarding the bioactive compounds of particular herbs and ingredients of the formulation should be collected from Database like UNPD (Universal natural product database), Zinc database, NPAtlas, NuBBEDB, Knapsack, CMAUP, TCM, COCONUT (Collection of open natural products), etc should be used, from these database one can search the molecular formula, drawn structure, InChI, InChI key, etc [5].
- After getting the structure of the bioactive compound from the above database in a .sdf file, the target of that compound is searched by using a special tool i.e. finding the target or found my target by using Binding DB (Binding database). This database helps to find out the exact or similar compounds. According to the degree of similarity score is given to that structure in which 1 is the highest score6.
- A target with a score of 1 is then chosen for further study.
- The protein symbol of the active compound is taken from UniProt using the UniProt IDs4.
- Protein class and tissue protein expression were gathered from the HPA database (Human Protein Atlas database) [4].

2.3. Network construction of herb and formulation

A schematic representation of the interaction of various entities called nodes is the Network. Nodes of the herb and formulation are as follows:

- Herb/ formulation name and its botanical and constituents of formulation botanicals.
- The biochemical constituents present in them
- The target of the bioactivities
- The corresponding tissue in which a particular bioactive expressed itself
- The tissue type in which the corresponding tissue belongs
- Target class

2.4. Graph Tool used to make Visual Network

Construction of the network can be done with Cystoscape 3.2.1, a Java-based open software, Gephi, or network plotting libraries in Python like NetworkX with Matplotlib.

3. Results and Discussion

Here the data about the herb Ashwgandha and formulation Trikatu is mentioned which helps researchers in understanding the process of discovering the novel compounds and explore the full biological potential of those Ayurvedic herbs and formulations in the future [6].

3.1. Ashwgandha (Withania somnifera L.)

The synonyms, properties, and actions of the herb Ashwagandha are mentioned in various Ayurvedic literature. The synonyms of the Ashwagandha are all the names of the horse as a prefix and fragrance as a suffix along with Varaha Karni, Varada, Balada, and Kustha Gandhini. Ashwagandha reduces increased Vata and Kapha cures vitiligo, edema, and waste, and acts as a tissue vitalizer and tonic. It is bitter and astringent in taste, hot in potency, and increases the quality and quantity of semen.

3.1.1. Ashwgandha's Mode of Action

Ashwgandha is Tikta (bitter), Kashaya (astringent) in taste with Sheeta Virya (hot potency), and Madhura Vipaka (post-digestive effect). As per Ayurveda Ashwgandha is Kapha- Vata Hara. Kapha Hara because of Tikata, Kashaya Rasa and

Ushana Virya, and Vata Hara because of Madhura Vipaka and Ushana Virya. Its Karma (actions) is Rasayana (rejuvenator), Shukrala (Aphrodisiac), Shwashara, Balya (strength promoting activity, Brihaniya (increase body weight), etc. Due to these actions, it is indicated in Bala Shosha (emaciation in children), Anidra (insomnia), Shwasa Roga (Bronchial asthma), Kshya Roga (consumption), Garbha Dharana, Bandhyatva (conception, sterility), etc [7].

Here we will discuss the ethnopharmacological network of Ashwagandha which elucidates its Rasayana properties:

3.1.2. Network Construction

Table 1. Major Bioactive Compounds in Ashwagandha.

Withanolides	Alkaloids	Sitoindosides	Other Compounds*
Withaferin A	Anaferine	Sitoindoside IX	Somniferine
Withanolide A	Anahygrine	Sitoindoside X	Somniferinine
Withanolide B	Cuscohygrine		Somnine
Withanone	Tropine		Somniferin
Withanoside IV	Withanine		5-Dehydroxy withanolide R
Withanoside V			Withasomniferin-A
Withanolide D			
Withanolide E			
Withanolide G			

Table 2. Predominantly active compounds from above mentioned bioactive compounds and their targets.

Predominant active compound	Targets
Withaferin A	NF-κB, vimentin, heat shock proteins
Withanolide A	PPARγ, MAPK, NF-κB
Withanolide D	β-tubulin, heat shock proteins
Withanoside IV	Acetylcholinesterase, NMDA receptors
Somniferine	- GABA receptors

Table 3. Ashwgandha Targets and associated diseases.

NF- κB	Involved in inflammatory responses, cancer
Vimentin	Involved in cancer metastasis
Heat shock proteins	stress response, cancer
PPARγ	Adipose tissue, liver, muscle (metabolic disorders, diabetes)
MAPK	Ubiquitous (involved in cell proliferation, cancer)
β-tubulin	Ubiquitous (cell division, cancer)
Acetylcholinesterase	Brain (Alzheimer's disease)
NMDA receptors	Brain (neurodegenerative diseases)
GABA receptors	Brain (anxiety, epilepsy)

3.1.3. Tissue distribution of Ashwagandha targets

The tissue distribution of Ashwagandha (Withania somnifera) targets and their interactions with its active compounds can be understood through network pharmacology, focusing on specific pathways and cellular targets in different tissues. Here's how the compounds Withaferin A, Withanolide A, Withanolide D, Withanoside IV, and Somniferine interact with various molecular targets in the body:

3.1.3.1. Brain & Nervous System

Compounds: Withanolide A, Withanolide D, Somniferine.

Targets: NMDA receptors: Modulates glutamatergic signaling, enhancing neuroplasticity and cognition.

GABA receptors: Enhances inhibitory neurotransmission, promoting anxiolytic and sedative effects.

Acetylcholinesterase: Inhibits enzyme activity, improving cholinergic function, enhancing memory, and preventing neurodegeneration (linked to Alzheimer's disease).

Effects: Cognitive enhancement, neuroprotection, anti-anxiety effects, and memory improvement.

Tissues: Brain (hippocampus, cortex).

3.1.3.2. Immune & Inflammatory System

Compounds: Withaferin A, Withanolide A.

Targets: NF-κB: Inhibits NF-κB, a key regulator of inflammation and immune response, reducing pro-inflammatory cytokines and oxidative stress.

MAPK: Modulates the mitogen-activated protein kinase (MAPK) signaling pathway, involved in inflammation and cell stress responses.

Effects: Anti-inflammatory, immunomodulatory, and antioxidant properties.

Tissues: Immune cells (macrophages, neutrophils), inflammatory sites (joint tissues, skin).

3.1.3.3. Musculoskeletal System

Compounds: Withaferin A, Withanolide D.

Targets: Vimentin: Withaferin A disrupts vimentin, an intermediate filament protein involved in cellular integrity and stress response, leading to anti-cancer and anti-inflammatory effects.

B-tubulin: Inhibits microtubule assembly, affecting cell division and anti-cancer properties.

Effects: Anti-inflammatory, supports muscle repair, reduces joint inflammation.

Tissues: Muscle, cartilage, connective tissue.

3.1.3.4. Endocrine System (Metabolic Regulation)

Compounds: Withanolide A, Withanoside IV.

Targets: PPARγ (Peroxisome Proliferator-Activated Receptor Gamma): Activates PPARγ, which is crucial in regulating glucose metabolism, lipid homeostasis, and insulin sensitivity.

Effects: Improves insulin sensitivity, supports weight management, and has anti-diabetic effects.

Tissues: Adipose tissue, liver, muscle (metabolic tissues).

3.1.3.5. Stress Response (Heat Shock Proteins)

Compounds: Withaferin A.

Targets: Heat Shock Proteins (HSPs): Modulates the expression of heat shock proteins, particularly HSP70, which help protect cells from stress and maintain protein homeostasis.

Effects: Cyto-protection enhances cell survival under stress and anti-cancer potential.

Tissues: Cellular stress response across multiple tissues (brain, heart, muscles).

3.1.3.6. Cardiovascular System

Compounds: Withaferin A, Withanolide A.

Targets: NF-κB and MAPK: Modulates these pathways, reducing inflammation and protecting cardiovascular health.

PPARγ: Improves lipid metabolism, reducing cholesterol and enhancing cardiovascular protection.

Effects: Cardioprotective effects, anti-inflammatory properties, regulation of lipid levels.

Tissues: Heart, blood vessels, and liver.

3.2. Trikatu

The properties and actions of the formulation Trikatu are mentioned in various Ayurvedic literatures. Trikatu is a combination of three bitter herbs in equal quantity i.e. Saunth (Zingiber officinale), Maricha (Piper nigrum), and Pippali (Piper longum). Trikatu is used to cure various disorders like digestive impairment, skin disorders, obesity, and diseases of the nose and throat. Trikatu as a formulation is hot in potency (Ushana Virya) light (Laghu) and dry (Ruksha) in nature8. Trikatu helps in achieving various therapeutic goals as it enhances the bioavailability of various phytoconstituents and synthetic drugs if incorporated with them. Here we will discuss the ethnopharmacological network of Trikatu [8].

3.2.1. Network Construction

Name of formulation- Trikatu

Ingredients

Saunth- Zingiber officinale Roscoe

Maricha- Piper nigrum L.

Pippali- Piper longum L.

Table 4. Major Bioactive Compounds in Trikatu.

Saunth	Maricha	Pippali
Gingerol	Piperine	Piperlongumine
Paradol	Piperidine	Piperine
Zingiberene	Chavicine	Piperlonguminine
Curcumene	Piperettine	Sesamine
Shogaol	Piperanine	Sylvatine
Cineole	Pipercide	Mristicin
Zingerone	Guineensine	Lignans

6- Dehydrogingerdione	Wisanine	Sesamin
6- Gingerdiol	N-isobutylamide	N- Isobutyl deca-trans-2, trans-4 dienamide
Beta-bisabolene	Beta-caryophyllene	Retrofractamide A
Farnesene	Dihydrocubebine	Retrofractamide B
Camphene	N- Isobutyl deca-trans-2, trans-4 dienamide	Sylvamide
Neral	N- Isobutyl eicosa-trans-2, trans-4 dienamide	Longamide
Geraniol	Sarmentine	Methyl piperate
Terpinen-4-ol	Myrcene	Sesamolin
Alpha-pinene	Limonene	Palmitic acid
Linalool	Sabinenne	Terpinen-4-ol
Citral	Pinene	Perylenequinones
	Camphene	
	Tetrahydropiperic acid	

Table 5. Predominantly active compounds from above mentioned bioactive compounds of Trikatu.

Saunth	Maricha	Pippali
Gingerol	Piperine	Piperlongumine
Shogaol	Piperidine	Piperine
Zingiberene	Chavicine	Piperlonguminine
Zingerone		Sesamine

3.2.2. Tissue Distribution of Trikatu Targets

Table 6. Piperlongumine Targets.

Bioactive	Tissue targeted	Role
Nrf2 (Nuclear factor erythroid 2-related factor 2)	Kidney, lungs, brain, liver	Regulates antioxidant response, and detoxification enzymes.
Keap 1 (Kelch-like ECH-associated protein 1)	Liver, lungs, kidney	Regulate Nrf2 by targeting it for degradation.
TRPV1	Sensory neurons, skin, urinary bladder	Mediates pain and heat sensation

Table 7. Piperine Targets.

Bioactive	Tissue targeted	Role
CYP3A4	Liver, intestine	Metabolize xenobiotics and various drugs
P-gp (P-glycoprotein)	Brain (blood-brain barrier), liver, kidney, intestine	Drug efflux transporter
TRPV1	Sensory neurons, skin, urinary bladder	Mediates pain and heat sensation

Table 8. Piperlonguminine Targets.

Bioactive	Tissue targeted	Role
COX-2	Inflammatory sites, Brain, Kidney	Produce prostaglandins involved in inflammation and pain
iNOS (Inducible Nitric Oxide Synthase)	Macrophages, liver, heart	Produce nitric oxides during immune response and inflammation.
TRPV1	Sensory neurons, skin, urinary bladder	Mediates pain and heat sensation

Table 9. Gingerol Targets.

Bioactive	Tissue targeted	Role
NF-κB (Nuclear Factor kappa-light-chain-enhancer of activated B cells)	Immune cells, liver, brain	Regulates immune response, inflammation, and cell survival
MAPK (Mitogen-Activated Protein Kinases)	Widely distributed in various tissues including the brain, heart, liver	Involved in cell signaling, growth, and differentiation
5-HT3 (Serotonin receptor 3)	GIT, Centrala, and Peripheral nervous system	Mediates neurotransmission, involved in vomiting and nausea.

Table 10. Shogaol Targets.

Bioactive	Tissue targeted	Role
TRPV1 (Transient Receptor Potential Vanilloid 1)	Skin, urinary bladder, sensory neurons	Mediates pain and heat sensation
5-HT3 (serotonin receptor 3)	Central and peripheral nervous system, gastrointestinal tract	Involved in cell signaling, growth, and differentiation
COX-2	Inflammatory sites, brain, kidney	Produce prostaglandins involved in inflammation and pain

Table 11. Zingerone Targets.

Bioactive	Tissue targeted	Role
TRPV1 (Transient Receptor Potential Vanilloid 1)	Skin, urinary bladder, sensory neurons	Mediates pain and heat sensation
NF-κB (Nuclear Factor kappa-light-chain-enhancer of activated B cells)	Immune cells, liver, and brain	Regulates immune response, cell survival, inflammation
PPARγ (Peroxisome Proliferator-Activated Receptor Gamma)	Adipose tissue, liver, Muscle	Insulin sensitivity, inflammation, regulates metabolism

Table 12. Some other targets of Trikatu are as follows.

Active	Bioactive	Tissue targeted	Role
Zingiberene	Sesquiterpene	Liver, muscles, fat tissues, lungs, spleen	Anti-inflammatory, antioxidant, gastroprotective
Piperine	Alkaloid	Liver, kidney, brain, GIT, crosses BBB, fat tissues	CNS activity, anti-inflammatory, weight loss, digestive health, bioavailability enhancer
Piperidine	Volatile alkaloid	Liver, GIT, in neural tissues	Nervous system modulator,

			anti-inflammatory, anti-microbial
Chavicine	Isomer of piperine	Liver, GIT, muscles	Bronchodilator, anti-inflammatory
Sesamine	Lignan	Liver, adipose tissue, brain, nervous system	Lipid metabolism, antioxidant, anti-inflammatory

3.3. Results

3.3.1. Network Mapping of Ashwagandha

Here is a network mapping of Ashwagandha (Withania somnifera) showing its active compounds, their targets, target tissues, and associated diseases. This visualization helps illustrate how Ashwagandha's active compounds interact with various biological targets and the potential therapeutic effects on different tissues and diseases.

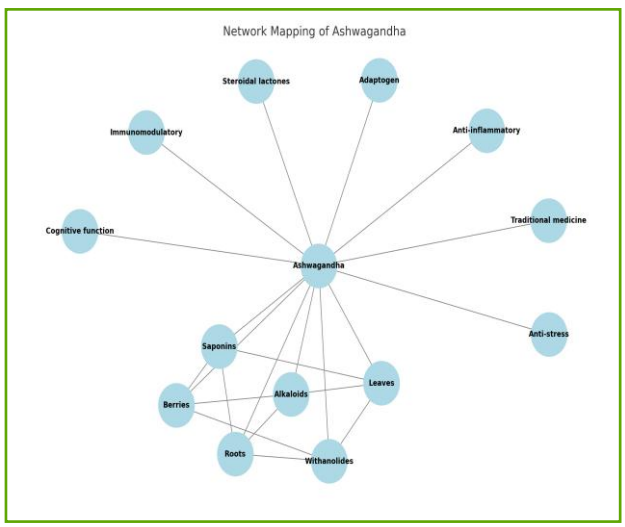

Figure 1. Network Mapping of Ashwagandha.

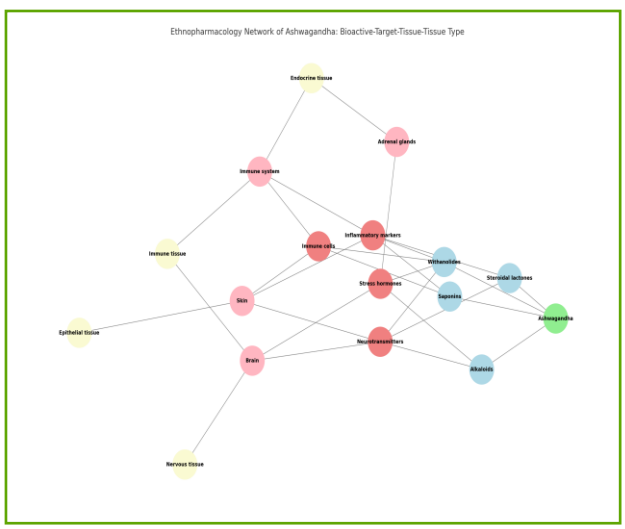

Figure 2. Ethnopharmacology Network of Ashwagandha: Bioactive-Target-Tissue-Tissue Type.

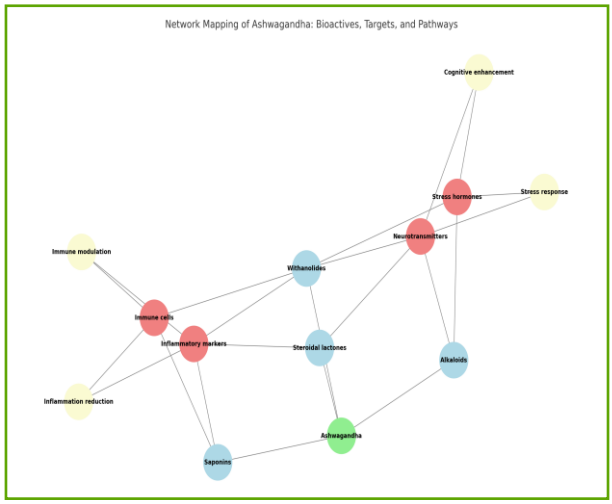

Figure 3. Network Mapping of Ashwagandha: Bioactives, Targets and Pathways.

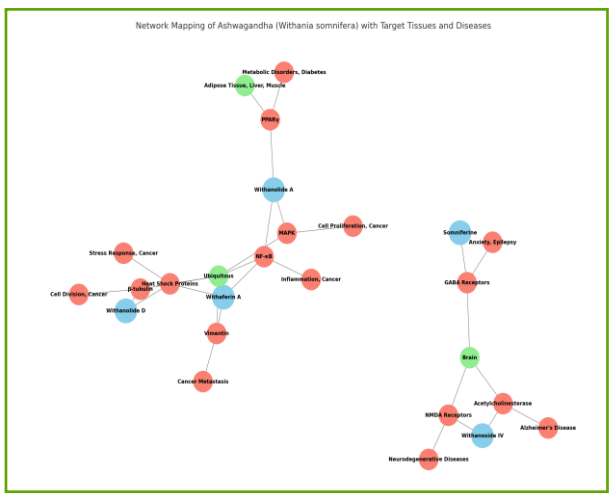

Figure 4. Network Mapping of Ashwagandha (Withania somnifera) with Target Tissues and Diseases.

3.3.2. Network Mapping of Trikatu

Here is a network mapping of Trikatu showing its active compounds, their targets, target tissues, and associated diseases. The different node colors represent compounds (sky blue), tissues (light green), and diseases (salmon). This visualization helps illustrate how Ashwagandha's active compounds interact with various biological targets and the potential therapeutic effects on different tissues and diseases.

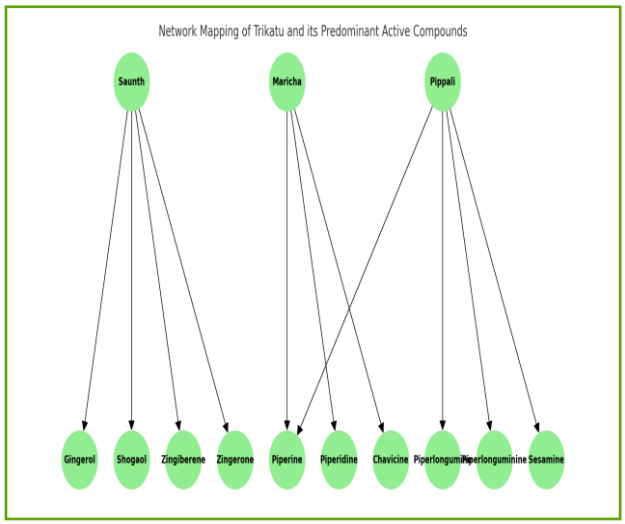

Figure 5. Network Mapping of Trikatu and its Predominant Active Compounds.

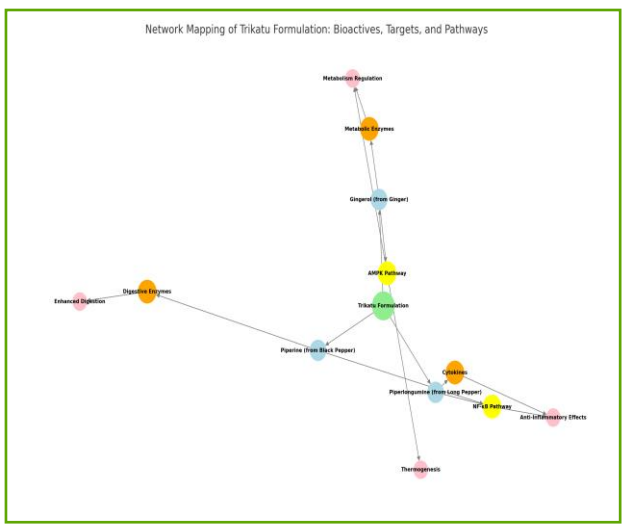

Figure 6. Network Mapping of Trikatu Formulation: Bioactives, Targets, and Pathways.

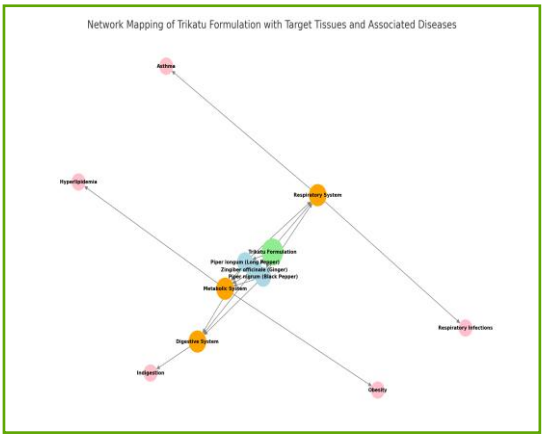

Figure 7. Network Mapping of Trikatu Formulation with Targets Tissues and Associated Diseases.

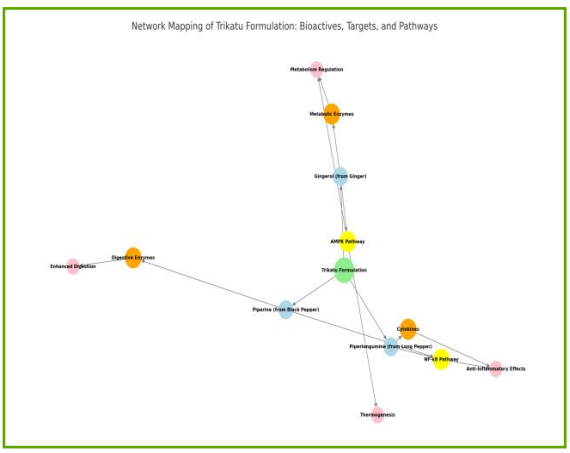

Figure 8. Network Mapping of Trikatu Formulation: Bioactives, Targest, and Pathways.

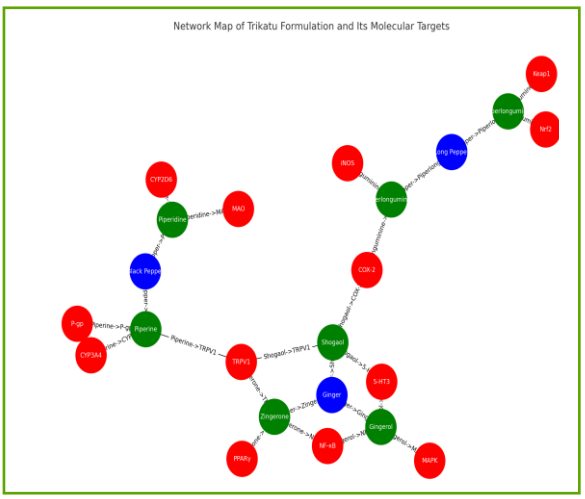

Figure 9. Network Map of Trikatu Formulation and its Molecular Targets.

4. Conclusions and Future Scope

Network pharmacology provides a holistic approach to understanding the complex interactions between bioactive compounds, molecular targets, biological pathways, and therapeutic effects. Unlike traditional pharmacology, which often focuses on single drug-target interactions, network pharmacology recognizes that herbal formulations (eg., Trikatu) and natural compounds like those found in traditional systems act on multiple targets simultaneously. This makes it particularly suitable for studying complex herbal formulations like Trikatu. Understanding network pharmacology gives enormous benefits. As per the new syllabus of NCISM for graduates of BAMS (Bachelor of Ayurvedic Medicine and Surgery), a Network pharmacology topic is added. By utilizing network mapping, scholars, and researchers can visualize how bioactive compounds (e.g., Piperine, Piperlongumine, Gingerol) interact with multiple targets, such as enzymes, receptors, and cellular pathways, influencing various tissues and cell types. For instance, Trikatu's bioactive may target receptors involved in digestion, inflammation, and metabolism, affecting tissues like the intestines, lungs, and adipose tissue. This approach has significant implications in drug discovery and development, as it helps in understanding the synergistic effects of multi-component herbal formulations. It also aids in identifying potential mechanisms of action, predicting side effects, and ensuring more efficient and safer therapeutic interventions. Thus, network pharmacology bridges traditional herbal knowledge and modern molecular biology, fostering a more comprehensive understanding of complex formulations and their roles in disease management. Below are the advantages of Network pharmacology.

4.1. Multi-Component Analysis

Evaluates the synergistic effects of multiple components in Ayurvedic formulations, reflecting the traditional holistic approach.

4.2. Pathway Integration

Maps the interaction of various herbal compounds with biological pathways, providing insights into their collective therapeutic effects.

4.3. Enhanced Efficacy and Safety

Optimized Combinations: Identifies optimal combinations of herbs that work synergistically, enhancing efficacy and reducing potential side effects.
Side Effect Prediction: Predicts possible adverse interactions between herbal components and their targets, improving the safety profile of Ayurvedic treatments.

4.4. Personalized Ayurvedic Treatments

4.4.1. Individual Type Therapies

Supports personalized medicine by considering individual variations in biological networks and responses to Ayurvedic formulations.

4.4.2. Biomarker Identification

Helps discover biomarkers that can predict a patient's response to specific Ayurvedic treatments, tailoring therapies to individual needs.

4.5. Drug Repositioning and Innovation

- New Applications for Herbs: Identifies new therapeutic uses for existing Ayurvedic herbs and formulations by exploring their effects on different biological networks.
- Cost-Effective Development: Reduces the time and cost associated with developing new Ayurvedic treatments by re-purposing existing herbs for new indications.

4.6. Understanding Ayurvedic Principles

- Dosha and Herb Interaction: Explores how different herbs influence the balance of Vata, Pitta, and Kapha doshas at a molecular level.
- Mechanistic Insights: Provides a deeper understanding of the mechanisms underlying traditional Ayurvedic practices, bridging the gap between ancient wisdom and modern science.

4.7. Integration with Modern Medicine

- Complementary Approaches: Facilitates the integration of Ayurvedic treatments with conventional medicine, enhancing overall patient care.
- Evidence-Based Validation: Provides a scientific basis for the efficacy of Ayurvedic formulations, supporting their acceptance and use in modern healthcare.

4.8. Sustainable Drug Development

- Natural Product Utilization: Promotes the use of sustainable, plant-based compounds in drug development, aligning with the eco-friendly principles of Ayurveda.
- Resource Conservation: Optimizes the use of natural resources by identifying the most effective and sustainable herbs and formulations.

4.9. Enhanced Research and Collaboration

Data Integration: Combines traditional Ayurvedic knowledge with modern biological data, creating comprehensive databases for future research and development.

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Conflict of Interest

Authors have no conflict of interest.

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