



Integrative Network Pharmacology of Ayurvedic Formulation-Trikatu: Analyzing Rasapanchaka Concepts with Advanced in Silico Tools

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Abstract

Indian Medical Systems (ISM) employ around 6,000 plant species in medicinal preparations, ranging from simple to highly complex formulations involving up to 100 ingredients. Over 350,000 such formulations are documented in the Traditional Knowledge Digital Library (TKDL). Ayurveda, a key branch of ISM, uses the principles of Dravyaguna Shastra and the Rasapanchaka framework— comprising *Rasa* (taste), *Guna* (properties), *Virya* (potency), *Vipaka* (post-digestive effect), and *Prabhava* (specific action)—to evaluate plant-based therapies. Network Pharmacology (NP) offers a systems-level approach, combining traditional knowledge with modern science to elucidate the multi-target mechanisms of such formulations.

This study applies NP to investigate Trikatu churna, a classical Ayurvedic formulation consisting of Shunthi (*Zingiber officinale*), Pippali (Piper longum), and Maricha (Piper nigrum). Using tools such as Cytoscape and other in silico methods, the research uncovers the network of interactions between Trikatu's bioactive compounds and disease-related targets. Findings highlight its traditional roles in enhancing digestion, metabolism, and the bioavailability of co-administered drugs. This integrative approach reinforces the scientific basis of Trikatu's therapeutic efficacy and supports further exploration of Ayurvedic formulations through network-based pharmacology.

Keywords: Ayurveda, Dravyaguna Shastra, Rasapanchaka, Network Pharmacology, Trikatu, Pharmacodynamics, Plant Drugs

1. Introduction

Ayurveda, the traditional medical system of India, has long relied on a rich pharmacopeia of medicinal plants, many of which are detailed in classical Ayurvedic texts. With the growing global interest in natural and plant-based therapies, there is increasing recognition of the value of these traditional medicines in contemporary healthcare. Ayurvedic formulations, often composed of multiple botanicals, offer unique therapeutic potential owing to their diverse chemical profiles and multi-targeted biological effects. However, the integration of such traditional knowledge into evidence-based medicine requires rigorous scientific validation of their safety, efficacy, and mechanisms of action (Mukherjee et al., 2017; Nair, 2018).



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Among the numerous formulations in Ayurveda, **Trikatu churna**—a classical combination of Shunthi (*Zingiber officinale*), Pippali (*Piper longum*), and Maricha (*Piper nigrum*)—has garnered considerable interest. Traditionally used to stimulate digestion, enhance metabolism, and detoxify the body, Trikatu is also believed to improve the bioavailability of other drugs and balance the three doshas (Vata, Pitta, and Kapha). Modern studies support its use in managing conditions such as respiratory disorders, obesity, joint pain, and gastrointestinal ailments (Kaushik et al., 2018; Krishniya et al., 2020; Sadanandan & Prasad, 2023). Its physicochemical and phytochemical properties have been studied to facilitate standardization and quality control (Saha et al., 2023).

Despite promising pharmacological evidence, the scientific understanding of how each component of Trikatu contributes to its overall therapeutic action remains incomplete. Research exploring its effects in animal models has highlighted its antioxidant, anti-inflammatory, and cytoprotective properties, particularly in the context of alcoholic liver disease (Sharma, 2022). However, there is a need for more comprehensive mechanistic studies, particularly in human models, to support its clinical application.

Network Pharmacology (**NP**) has emerged as a powerful tool to explore complex interactions between multiple compounds and biological targets. By integrating traditional knowledge with systems biology and computational modeling, NP enables the mapping of compound-target-pathway networks, offering insights into the multi-component, multi-target nature of Ayurvedic formulations (Sakle et al., 2020; Chandran et al., 2017). This approach is especially valuable for studying polyherbal formulations like Trikatu, which act on several physiological systems simultaneously.

This study employs a network pharmacology framework to investigate the pharmacological basis of Trikatu churna. Using databases and in silico tools, including Cytoscape, we identify the potential targets, pathways, and biological functions associated with its phytochemicals. ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profiling further supports the pharmacokinetic relevance of the identified compounds. By combining traditional knowledge with modern bioinformatics, this work aims to bridge the gap between Ayurveda and contemporary pharmacological research, offering a holistic understanding of Trikatu's therapeutic potential.

2. Materials and Methods

This study uses Ayurvedic concepts like Rasapanchaka and advanced in silico tools to explore the possible molecular targets of bioactive phytochemicals in the selected individual plant drugs and compound formulations. Figure 1 illustrates the overall methodology used to decipher the molecular action of selected herbs.

In this paper, we describe the methodology in detail. The approach begins with text mining of classical literature, followed by a set of effective and accurate methods to reveal the pharmacological basis of Trikatu's medicinal plants (Piper longum, Piper nigrum, and Zingiber officinale) and predict the potential bioactivity of their compounds. The steps involved include:



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2.1. Collection of Phytochemical Information:

An extensive dataset of phytochemicals present in *Trikatu*—comprising Shunthi (*Zingiber officinale*), Pippali (*Piper longum*), and Maricha (*Piper nigrum*)—was compiled through a comprehensive literature review and database mining. Relevant peer-reviewed publications were manually screened using the PubMed-NCBI database to identify reported bioactive compounds. Additionally, three curated phytochemical databases were consulted: **Dr. Duke's Phytochemical and Ethnobotanical Database**, **KNApSAcK**, and **IMPPAT (Indian Medicinal Plants, Phytochemistry And Therapeutics**). The retrieved phytochemical data were consolidated, and duplicate entries were removed to ensure nonredundancy. Detailed chemical properties and molecular identifiers of the final list of phytochemicals were further retrieved from the **PubChem** and **ChEMBL** databases for subsequent network pharmacology analysis.

2.2. Retrieval of Potential Targets

To identify potential human protein targets of the phytochemicals present in *Trikatu*, data were retrieved from multiple public repositories, including **BindingDB**, **ChEMBL**, **STITCH 5.0**, and the **Comparative Toxicogenomics Database** (**CTD**), with all queries limited to *Homo sapiens*. The retrieved target proteins were standardized by mapping them to their corresponding official gene symbols using the **UniProt** database.

2.3. Disease-Specific Target Annotation

To annotate disease relevance, the identified protein targets were cross-referenced with disease-related



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information in **DisGeNET** (v7.0) and the **Medical Subject Headings** (MeSH) database. This enabled the classification of targets associated with digestive system disorders, aligning with the traditional therapeutic applications of *Trikatu*.

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2.4. Network Construction and Analysis

A compound-target-disease interaction network was constructed to illustrate the pharmacological mechanisms of *Trikatu* in managing digestive system-related conditions. The network was built and visualized using **Cytoscape** (v3.9.1). Topological parameters such as degree, betweenness centrality, and closeness centrality were calculated to identify key bioactive compounds and hub targets. These were further analyzed to determine their relevance in the therapeutic action of *Trikatu*.

3. Results & Discussion

3.1. Active Molecules:

Database mining identified 234 molecules associated with Zingiber officinale, Piper longum, and Piper nigrum, consisting of 102, 33, and 69 molecules, respectively. Overlapping is shown in vandiagram below. The prevalence of molecules among botanicals is shown in Figure 2.



Figure 2: The count of overlapping molecules present in Zingiber officinale, Piper longum, and Piper nigrum

3.2. Possible Targets and Indications:

We identified 2,351 potential targets encoding 145 disease class indications. Among these, 36 diseases were related to digestive system disorders and were chosen for further study

3.3. Topology Analysis:

Molecules such as testosterone, capsaicin, l-ascorbic acid, acetic acid, eugenol, geraniol, glycine, dlarginine, pyrocatechol, and paroxetine showed distinct interactions with more than 30 targets. Similarly, CYP1A2, ALOX5, PTGS1, NFE2L2, TNF, and STAT3 also demonstrated distinct interactions with multiple molecules. The topology annotation revealed that Trikatu molecules highly interact with targets involved in digestive system diseases (see Figure 3).



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Figure 3: Trikatu-digestive system diseases network. Rectangles (azure blue, purple, and pink) represent molecules of Piper nigrum, Zingiber officinale, and Piper longum, respectively. Green circles are targets interacting with red V-shaped nodes representing disease classes.



Figure 4: The chart indicates that different disease classes have varying degrees of genetic influence.

Digestive system diseases and mental disorders appear to be the most genetically complex, with a large number of associated genes. This could reflect the wide range of conditions within these categories or the multifactorial nature of these diseases. Conversely, categories with fewer associated genes might represent either less complex genetic backgrounds or more specific conditions within those classes. Understanding the genetic basis of these diseases is crucial for developing targeted therapies and personalized medicine approaches.

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KEGG pathway annotation chart



Fig 5: KEGG pathway annotation chart:

The KEGG pathway analysis of Trikatu reveals its significant impact on digestion and metabolism. Trikatu, a traditional Ayurvedic formulation composed of Shunthi (Zingiber officinale), Pippali (Piper longum), and Maricha (Piper nigrum), shows robust involvement in several key metabolic pathways. Notably, it influences pathways related to carboxylic acid metabolism and amino acid metabolism. These pathways are crucial for the breakdown of nutrients and the conversion of food into energy and other essential compounds.

Carboxylic Acid Metabolic Process: This pathway, enriched in the analysis, is vital for the metabolism of fatty acids and other carboxylic acids. By enhancing this process, Trikatu aids in the efficient breakdown of fatty acids, which is essential for energy production and overall metabolic health.

Amino Acid Metabolism: Another significant pathway influenced by Trikatu, this process involves the synthesis and breakdown of amino acids, which are fundamental for protein synthesis, tissue repair, and various metabolic functions. Trikatu's impact on amino acid metabolism supports its traditional use in enhancing digestion and metabolic efficiency.

Additionally, the analysis highlights pathways involved in the response to xenobiotic stimuli, suggesting that Trikatu may help the body manage and detoxify foreign substances, further supporting its role in digestive health and metabolic processes.

Overall, KEGG pathway analysis underscores Trikatu's multifaceted effects on digestion and metabolism, aligning with its traditional uses and providing a molecular basis for its therapeutic benefits.





Figure 6: Pathway enrichment analysis

The bar plot illustrates the results of a pathway enrichment analysis, showing the significance of various biological pathways in the dataset. The x-axis represents the significance level, measured as $-\log 10(P)$, with higher values indicating more significant results. The y-axis lists the pathways that are enriched.

The most significant pathways include the "carboxylic acid metabolic process," "Pathways in cancer," and "response to xenobiotic stimulus." These processes have very low p-values, meaning they are highly enriched and likely play crucial roles in the biological context being studied.

Digestion-related pathways, particularly those involved in metabolism, are also highlighted in the results. For instance, pathways like amino acid metabolism and carboxylic acid metabolic processes are crucial for breaking down nutrients and converting them into energy and other essential compounds. These pathways are not only fundamental to digestion but are also highly significant in the context of the study, suggesting that digestive processes may play a key role in the biological phenomena under investigation.

Other important pathways involve responses to environmental stimuli and various signaling events. Some pathways are associated with specific conditions, such as ADHD and autism or the nuclear receptor meta pathway.

Overall, these results highlight key biological processes, including digestion and metabolism, that are potentially central to the phenomena being investigated, whether it's a disease mechanism, a cellular response, or metabolic activity. Understanding these pathways is likely crucial for interpreting the underlying biology of the dataset.

Biological Interpretation

PPI Network & MCODE Components

R-HSA-416476|G alpha (q) signalling events|-100.0;hsa04080|Neuroactive ligand-receptor interaction|-100.0;R-HSA-373076|Class A/1 (Rhodopsin-like receptors)|-100.0

We conducted a GO enrichment analysis on each MCODE network to understand their biological significance. The analysis highlighted the following key terms, which were the most statistically significant:

• G alpha (q) Signaling Events: This term points to the role of G alpha (q) proteins in signaling pathways within cells. These pathways are crucial for various processes, including how hormones



are released and how smooth muscles in the digestive tract contract, which are important for digestion and metabolism.

- Neuroactive Ligand-Receptor Interaction: This term refers to how neurotransmitters and other signaling molecules interact with their receptors. These interactions are vital for regulating appetite, digestion, and energy balance, influencing how we process and use nutrients.
- Class A/1 (Rhodopsin-like Receptors): This term describes a large group of receptors that play significant roles in regulating digestive enzyme secretion and energy balance. These receptors help manage how our body processes food and maintains energy levels.

These terms shed light on the important biological functions related to digestion and metabolism, showing how different signaling pathways and receptor interactions are involved in these processes.

Dravyaguna Rasapanchaka of ingredients of trikatu

Dravyaguna Rasapanchaka (the five-fold pharmacological evaluation) is a framework used in Ayurveda to analyze the properties of herbs and substances based on their effects on the body. This evaluation includes **Rasa** (taste), **Virya** (potency), **Vipaka** (post-digestive effect), **Guna** (qualities), and **Prabhava** (special effect). To interpret this concept with references from different journal papers, let's examine how these properties are described and supported by modern research:

1. Rasa (Taste)

The pungent taste of Trikatu ingredients, including black pepper and long pepper, is consistent with their known digestive stimulating properties. Pungent substances are traditionally used in Ayurveda to enhance digestive fire (Agni) and promote metabolic processes.

2. Virya (Potency)

The hot potency of the Trikatu ingredients aligns with their ability to increase metabolic rates and improve digestive efficiency. The hot nature aids in balancing digestive processes and overcoming issues like coldness or dampness in the digestive tract.

3. Vipaka (Post-Digestive Effect)

Studies on Zingiber officinale (ginger) reveal that its post-digestive effect is sweet, which aligns with its ability to balance digestive heat and promote overall gastrointestinal health **4**.

4.Guna (Qualities)

In Ayurveda, *Guna* refers to the qualities of a substance that influence its effects on the body and mind. Trikatu, an Ayurvedic blend made from black pepper (*Piper nigrum*), long pepper (*Piper longum*), and dried ginger (*Zingiber officinale*), is recognized for its therapeutic properties. Its pungent taste stimulates digestion, making it effective for treating issues like tastelessness and digestive problems. The hot nature of Trikatu helps balance the *Vata* and *Kapha* doshas, while increasing *Pitta*, which makes it useful for respiratory conditions such as asthma and chronic rhinitis. The light and dry qualities further support its effectiveness in managing metabolic disorders, obesity, and conditions like sinusitis and skin diseases.

Trikatu is especially beneficial for digestive health due to its ability to stimulate digestive enzymes and increase bile flow, which enhances nutrient absorption and alleviates indigestion and bloating. It also helps clear toxins from the digestive system, promoting a healthy gut environment. Modern research supports these traditional uses, showing that Trikatu can enhance the bioavailability of various natural and synthetic drugs, making treatments more effective. In addition to its digestive benefits, Trikatu is known for its immunomodulatory, antiviral, expectorant, carminative, hypolipidemic, hypoglycemic,



antiemetic, and anti-inflammatory properties, making it a valuable remedy for a wide range of health issues. (Kaushik et al., 2018)

5. Prabhava (Special Effect)

The concept of "Prabhava" in Ayurveda refers to the unique and specific effects of a substance that go beyond its taste, quality, potency, or post-digestive effect. In the case of Trikatu—a blend of black pepper, long pepper, and ginger—Prabhava plays an important role. Trikatu is believed to enhance the absorption and effectiveness of other medicines by stimulating digestive enzymes, improving metabolism, and helping active ingredients penetrate deeper, which boosts their overall impact.

This special effect of Trikatu highlights its importance in Ayurvedic medicine, especially for digestion and nutrient absorption. Traditional Ayurvedic interpretations of Trikatu's ingredients, now supported by modern research, confirm the benefits of its pungent taste, hot potency, sweet post-digestive effect, and light, dry qualities. These align with its known ability to enhance digestion, metabolism, and overall health. (Joshi et al., 2024)

The interaction between components of dravyaguna rasapanchaka of ingredients of trikatu (*Shunthi* (*Zingiber officinale*), *Pippali (Piper longum*) and *Maricha (Piper nigrum*)) and their interaction with the various disease conditions was developed



Figure 7: Trikatu- Dravyaguna rasapanchaka -diseases network. Pink, purple and dark green circles: Trikatu- (*Shunthi, Pippali* and *Maricha*); Pink, purple and dark green rectangles: Ayurvedic properties of the ingredients of trikatu; light green circles: *karmas* – pharmacological actions as per Ayurveda; Red arrow heads: disease actions as per Ayurveda; pink triangles: actions on tridoshas- increase & decrease of vata, pitta and kapha doshas respectively (Vatakara, Vatahara, Pittakara, Pittahara, Kaphakara & Kaphahara) 11

The interaction between various parameters of dravyaguna rasapanchaka of *Shunthi* (*Zingiber officinale*), *Pippali* (*Piper longum*) and *Maricha* (*Piper nigrum*)) and their interaction with the various disease conditions was also developed



Dravyaguna Network of Zingiber officinale Based on Rasapanchaka



Fig 8: Dravyaguna Network of Shunti

The dravyaguna properties of Shunthi (*Zingiber officinale*) has around 311 probable disease targets linked to 15 major functional diseases due to properties linked to increase Vata (16), Pitta (62), Kapha (45) targets.

Shunthi, commonly known as ginger (Zingiber officinale), is a highly regarded herb in Ayurvedic medicine with extensive therapeutic potential. It is known for its wide-ranging effects on the body, impacting approximately 311 probable disease targets. This extensive influence is linked to its ability to address 15 major functional disease categories. Shunthi's properties can increase the doshas—specifically, Vata, Pitta, and Kapha—with 16 effects on Vata, 62 on Pitta, and 45 on Kapha. This broad range of actions allows Shunthi to address various imbalances and health issues related to these doshas. Its impact on Pitta, in particular, reflects its role in enhancing digestive fire and metabolism, making it valuable for treating conditions associated with heat and inflammation.

Maricha Network has around 172 probable disease type targets



Fig 9: Dravyaguna Network of Maricha (Piper nigrum L.)

Maricha, or black pepper, is a versatile herb in Ayurveda known for its impact on the body's tissues and doshas. Maricha (black pepper) has a more focused range of effects. It influences around 33 different tissue functions, or Dhatukarma, with properties that both increase and decrease doshas. Maricha



increases Vata and Pitta with 5 and 11 targeted actions respectively, supporting functions related to movement, digestion, and heat. Additionally, it helps decrease excess Vata and Kapha with 6 and 11 targeted actions respectively. This dual functionality allows Maricha to help balance doshas, addressing issues related to dryness, congestion, and excess moisture. While Shunthi has a broader impact on various disease targets, Maricha provides more specific modulation of doshas, complementing the therapeutic effects of Shunthi. This balanced approach makes Maricha a valuable herb for both stimulating and harmonizing various bodily functions, supporting overall health by addressing dosha imbalances.

Dravyaguna Network of Pippali (Piper longum)



Fig 10: Dravyaguna Network of Pippali (Piper longum)

Pippali, or Piper longum, is a remarkable herb in Ayurvedic medicine, known for its diverse therapeutic effects. It impacts around 73 different tissue functions (Dhatukarma) within the body, influencing overall health and balance. Pippali's properties have a dual effect on the three doshas—Vata, Pitta, and Kapha. It can both increase and decrease these doshas depending on the context and need. Specifically, it has properties that can raise Vata and Pitta, contributing to their respective qualities of movement and heat. Conversely, it also works to balance and reduce excess Vata, Pitta, and Kapha, which helps in managing conditions related to dryness, heat, and moisture.

The herb's extensive range of effects extends to its ability to address approximately 253 different disease types. This broad therapeutic potential underscores Pippali's versatility in treating a wide array of health issues. By influencing the doshas and tissues in multiple ways, Pippali plays a significant role in restoring balance and promoting overall well-being.

Conclusion

Developing traditional medicine with a focus on safety, efficacy, and quality is crucial not only for preserving this heritage but also for rationalizing the use of herbal medicine in healthcare. This kind of study is useful for Ayurveda drug development as it helps manufacturers and clinicians explain the structure and functions of Ayurvedic formulations in terms of modern pharmacology. The network pharmacology approach used in this study enables the design of novel herbal combinations derived from classical formulations (with Ayurveda pharmacology logic—Dravyaguna Rasapanchaka) for new disease



manifestations. This approach provides a pragmatic connection between new etiopathology and specific targets, offering a transdisciplinary perspective that combines systemic and molecular knowledge for interpreting complex Ayurvedic poly-herbal formulations. The results provide reliable data and research leads for experimental studies and drug discovery.

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