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Review Article

GUT MICROBIOME-ASSOCIATED MECHANISMS OF *SEERAKA RASAYANAM* IN DYSLIPIDEMIA: A SYSTEMS PHARMACOLOGY APPROACH

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ABSTRACT

Dyslipidemia is a major metabolic disorder associated with chronic inflammation, oxidative stress, endothelial dysfunction, and cardiovascular complications. Emerging evidence suggests that gut microbiota dysbiosis plays a critical role in lipid metabolic disturbances through mechanisms involving endotoxemia, microbial metabolites, and inflammatory signaling pathways. *Seeraka Rasayanam*, a traditional Siddha polyherbal formulation, mentioned in *Agathiyar kurunthirattu* contains multiple phytochemicals with potential microbiome-modulating and anti-inflammatory properties. **Objective**: The present study aimed to explore the gut microbiome-associated mechanisms of *Seeraka Rasayanam* in dyslipidemia using a microbiome-centered systems pharmacology approach. **Materials and Methods**: The phytochemical constituents of *Seeraka Rasayanam* were identified through literature mining and phytochemical databases. Microbiome-associated phytochemicals were analyzed for their potential interactions with gut microbial communities, microbial metabolites, and host inflammatory pathways. Literature-based systems pharmacology integration was performed to identify microbiome-related signaling pathways implicated in dyslipidemia. **Results**: Major phytochemicals including piperine, thymoquinone, gingerol, gallic acid, plumbagin, and piperlongumine demonstrated potential associations with beneficial gut microbial populations such as lactobacillus, bifidobacterium, akkermansia and roseburia species. These interactions were linked with enhanced production of microbial metabolites including butyrate, propionate, acetate, and secondary bile acids. Integrated pathway analysis revealed potential modulation of TNF, NF-κB, IL-17, PPAR, PI3K–Akt, and AGE–RAGE signaling pathways associated with inflammation, oxidative stress, endothelial dysfunction, and lipid metabolism. **Conclusion**: The findings suggest that *Seeraka Rasayanam* may exert anti-dyslipidemic effects through modulation of gut microbiota-associated inflammatory and metabolic pathways. The proposed microbiome-centered systems pharmacology framework provides a mechanistic basis for future experimental validation of Siddha formulations in metabolic disorders.

INTRODUCTION

Dyslipidemia is a multifactorial metabolic disorder characterized by abnormal levels of serum lipids including elevated total cholesterol, triglycerides, low-density lipoprotein cholesterol, and reduced high-density lipoprotein cholesterol.

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Dyslipidemia is considered a major risk factor for cardiovascular diseases, atherosclerosis, metabolic syndrome, obesity, and non-alcoholic fatty liver disease. Although conventional lipid-lowering therapies are widely used, long-term management remains challenging due to adverse effects, residual cardiovascular risk, and metabolic complications.

Recent advances in microbiome research have demonstrated that gut microbiota plays a central role in metabolic homeostasis and cardiovascular health. Alterations in gut microbial composition, commonly referred to as gut dysbiosis, contribute significantly to chronic low-grade inflammation, oxidative stress,

endotoxemia, and lipid metabolic disturbances. Increased intestinal permeability permits translocation of lipopolysaccharides into systemic circulation, resulting in activation of inflammatory pathways including tumor necrosis factor (TNF), nuclear factor kappa B (NF-κB), interleukin-17 (IL-17), and oxidative stress-associated signaling cascades.

Gut microbiota also regulates lipid metabolism through production of microbial metabolites such as short-chain fatty acids (SCFAs), secondary bile acids, and indole derivatives. SCFAs including butyrate, acetate, and propionate contribute to maintenance of intestinal barrier integrity, modulation of inflammatory signaling, insulin sensitivity, and regulation of lipid homeostasis. Disturbances in microbial metabolite production have been strongly associated with dyslipidemia and atherosclerotic progression.

Traditional Siddha medicine emphasizes the role of digestive balance, metabolic regulation, and humoral equilibrium in disease management. *Seeraka Rasayanam* is a Siddha polyherbal formulation traditionally used for digestive and metabolic disorders. The formulation contains multiple medicinal ingredients including Cuminum cyminum, Nigella sativa, Zingiber officinale, Piper species, Phyllanthus emblica, and other phytochemically rich medicinal substances possessing antioxidant, anti-inflammatory, digestive, and metabolic regulatory properties.

Several phytochemicals present in *Seeraka Rasayanam* such as piperine, thymoquinone, gingerol, gallic acid, and plumbagin have been reported to influence gut microbial composition and inflammatory signaling pathways. However, the gut microbiome-associated mechanisms of *Seeraka Rasayanam* in dyslipidemia remain unexplored.

Therefore, the present study aimed to investigate the potential microbiome-associated mechanisms of *Seeraka Rasayanam* in dyslipidemia using a microbiome-centered systems pharmacology approach integrating phytochemicals, gut microbes, microbial metabolites, and host inflammatory pathways.

MATERIALS AND METHODS

Identification of Ingredients of *Seeraka Rasayanam*

The ingredients of *Seeraka Rasayanam* were collected from Siddha classical literature and standardized using botanical nomenclature. The formulation consists of medicinal herbs including Cuminum cyminum, Nigella sativa, Zingiber officinale, Piper nigrum, Piper longum, Plumbago zeylanica, Terminalia bellirica, Phyllanthus emblica, Embelia ribes, Ferula asafoetida, Brassica juncea, and Indhuppu.

Phytochemical Identification

Major phytochemicals associated with the selected medicinal ingredients were identified through literature mining and phytochemical databases including PubChem and published scientific reports. Important phytochemicals included piperine, piperlongumine, thymoquinone, gingerol, gallic acid, plumbagin, embelin, cuminaldehyde, ferulic acid derivatives, and glucosinolates.

Literature-Based Gut Microbiome Mapping

Published studies describing phytochemical interactions with gut microbial communities were systematically reviewed. Gut microbial species associated with the identified phytochemicals were mapped based on reported microbiome modulation studies. Beneficial microbial populations including Lactobacillus spp., Bifidobacterium spp., Akkermansia muciniphila, Roseburia spp., and Faecalibacterium prausnitzii were included in the analysis.

Microbial Metabolite Integration

Microbial metabolites associated with gut microbiota modulation including butyrate, acetate, propionate, secondary bile acids, and indole derivatives were identified through literature-based systems integration. Functional roles of these metabolites in lipid metabolism and inflammatory signaling were analyzed.

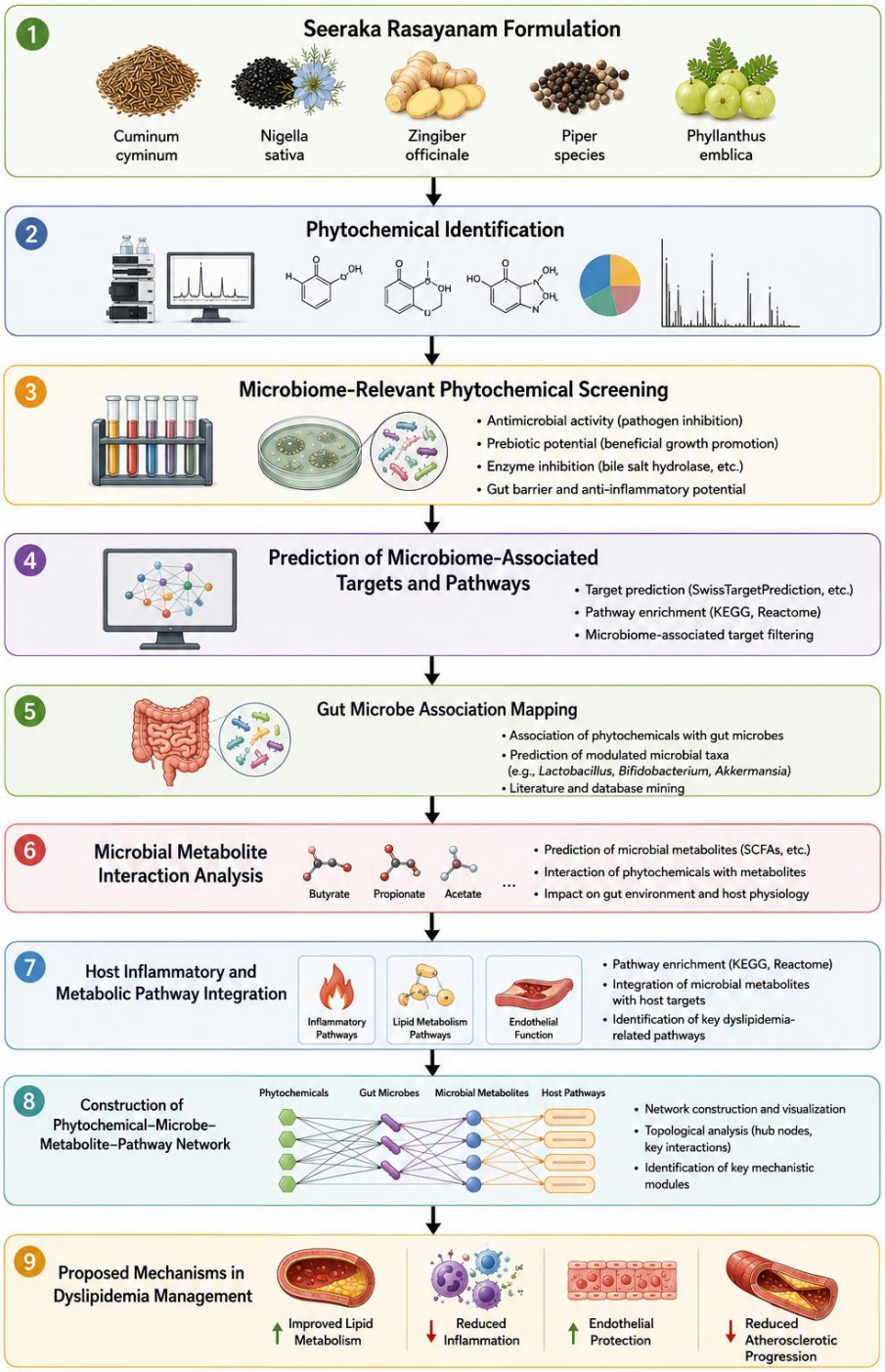
Systems Pharmacology and Pathway Analysis

Potential host signaling pathways associated with the identified phytochemicals and microbial metabolites were evaluated through literature-supported systems pharmacology analysis. Major pathways implicated in dyslipidemia including TNF signaling, NF-κB signaling, IL-17 signaling, PPAR signaling, PI3K–Akt signaling, AGE–RAGE signaling, and lipid-associated inflammatory pathways were integrated into the microbiome-centered mechanistic framework.

Construction of Integrated Interaction Network

A conceptual phytochemical–microbe–metabolite–pathway interaction framework was constructed to illustrate the potential host–microbe–metabolic interactions involved in the anti-dyslipidemic effects of *Seeraka Rasayanam*.

Figure: 1 Workflow of microbiome-centered systems pharmacology analysis of *Seeraka Rasayanam* in dyslipidemia



RESULTS

Ingredients and Major Phytochemicals of *Seeraka Rasayanam*

Seeraka Rasayanam contains multiple medicinal ingredients possessing diverse phytochemicals with potential microbiome-associated therapeutic relevance. Major phytochemicals identified from the formulation included piperine, thymoquinone, gingerol, gallic acid, plumbagin, embelin, piperlongumine, cuminaldehyde, ferulic acid derivatives, and glucosinolates.

The identified phytochemicals are known to possess antioxidant, anti-inflammatory, digestive, endothelial protective, and metabolic regulatory properties.

Table 1: Ingredients of *Seeraka Rasayanam*

S.No	Botanical Name	Common Name	Part Used
1	*Cuminum cyminum*	Cumin	Seed
2	*Nigella sativa*	Black cumin	Seed
3	*Zingiber officinale*	Dry ginger	Dried rhizome
4	*Piper nigrum*	Black pepper	Fruit
5	*Piper longum*	Long pepper	Fruit
6	*Piper longum*	Long pepper root	Root
7	*Plumbago zeylanica*	Leadwort	Root
8	*Terminalia bellirica*	*Belleric myrobalan*	Fruit
9	*Phyllanthus emblica*	Indian gooseberry	Fruit
10	*Embelia ribes*	False black pepper	Fruit
11	*Ferula asafoetida*	Asafoetida	Resin
12	*Brassica juncea*	Mustard	Seed
13	*Indhuppu*	Rock salt	-

Gut Microbiome Associations of Identified Phytochemicals

The phytochemicals identified from *Seeraka Rasayanam* demonstrated potential interactions with beneficial gut microbial populations. Piperine was associated with modulation of Lactobacillus and Bifidobacterium species, whereas thymoquinone demonstrated potential association with Akkermansia muciniphila and Bacteroides species.

Gallic acid and gingerol were linked with SCFA-producing bacteria including Roseburia and Faecalibacterium species. These microbial interactions may contribute to improvement of gut barrier integrity and suppression of dysbiosis-associated inflammation.

Table 2: Phytochemical–Microbe Interaction Table

Phytochemical	Source Herb	Gut Microbes Potentially Influenced	Potential Functional Effect
Piperine	Piper nigrum	Lactobacillus, Bifidobacterium	Improved gut barrier and anti-inflammatory effects
Piperlongumine	Piper longum	Anti-inflammatory microbial shifts	Reduced endotoxemia
Thymoquinone	Nigella sativa	Akkermansia, Bacteroides	Gut barrier protection
Gingerol	Zingiber officinale	Faecalibacterium, Lactobacillus	SCFA enhancement
Gallic acid	Phyllanthus emblica	Roseburia, Bifidobacterium	Butyrate production
Plumbagin	Plumbago zeylanica	Oxidative stress-associated microbiota	Antioxidant effects
Embelin	Embelia ribes	Bacteroides spp.	Lipid metabolic regulation
Cuminaldehyde	Cuminum cyminum	Digestive microbiota	Improved digestion and metabolism.
Ferulic acid derivatives	Ferula asafoetida	SCFA-producing bacteria	Anti-inflammatory modulation
Glucosinolates	Brassica juncea	Prevotella, Bacteroides	Bile acid metabolism regulation

Microbial Metabolite and Host Pathway Integration

Beneficial microbial metabolites including butyrate, acetate, propionate, secondary bile acids, and indole derivatives were integrated into the proposed mechanistic framework.

Butyrate and propionate were associated with regulation of lipid metabolism, inflammatory suppression, and maintenance of intestinal barrier integrity. Secondary bile acids demonstrated potential relevance in cholesterol metabolism and gut–liver axis regulation.

Table 3: Microbial Metabolite-Host Pathway Interaction Table

Microbial metabolite	Major microbial sources	Host pathways potentially regulated	Functional relevance in dyslipidemia
Butyrate	Lactobacillus, Roseburia, Faecalibacterium	PPAR, AMPK, NF-κB suppression	Anti-inflammatory and lipid regulation
Propionate	Bacteroides spp.	Lipid metabolism pathways	Cholesterol homeostasis
Acetate	Bifidobacterium spp.	PI3K–Akt signaling	Metabolic regulation
Secondary bile acids	Bacteroides spp.	PPAR and FXR signaling	Cholesterol metabolism
Indole derivatives	Gut commensal bacteria	IL-17 and immune pathways	Immune homeostasis

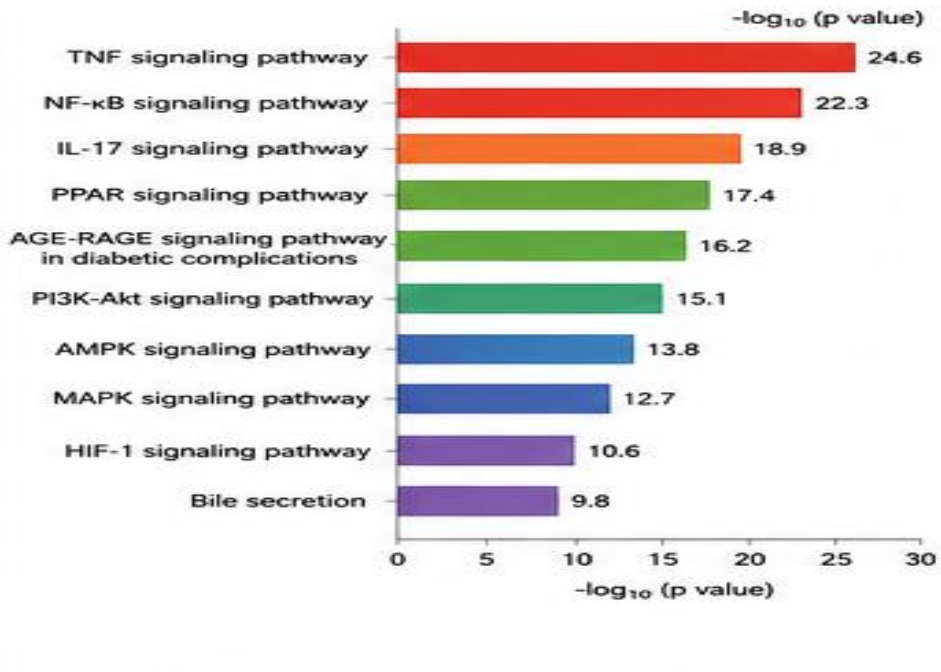
Microbiome-Associated Pathway Regulation

Integrated pathway analysis revealed that the identified phytochemicals and microbial metabolites were predominantly associated with inflammatory and metabolic pathways implicated in dyslipidemia.

The major pathways included:

- TNF signaling pathway
- NF-κB signaling pathway
- IL-17 signaling pathway
- PPAR signaling pathway
- PI3K–Akt signaling pathway
- AGE–RAGE signaling pathway
- and lipid and atherosclerosis pathway

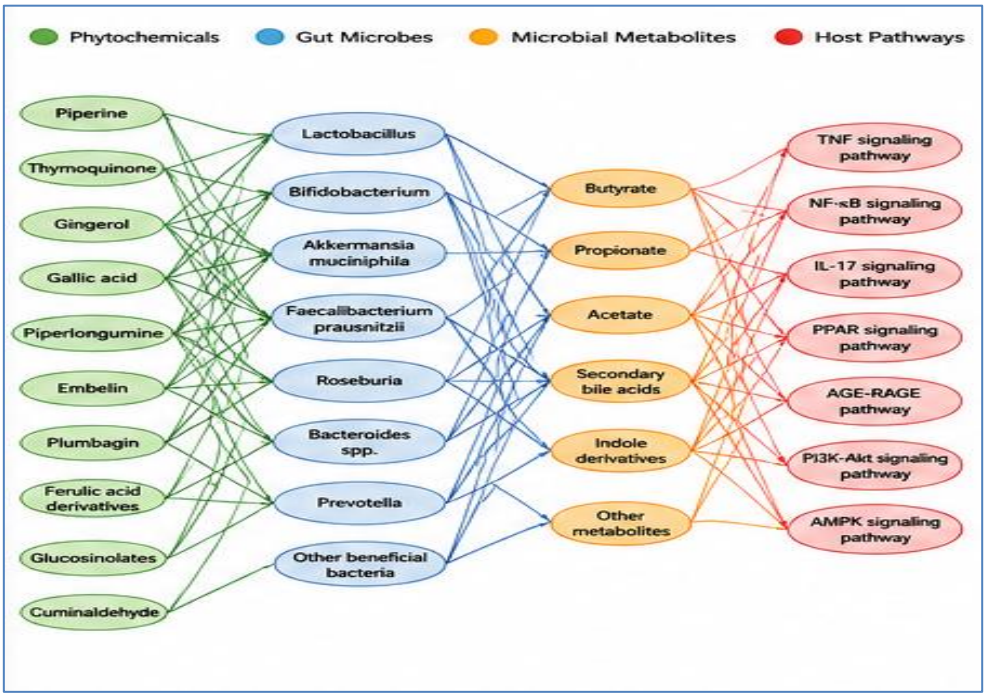
These pathways are strongly associated with metabolic endotoxemia, oxidative stress, endothelial dysfunction, chronic inflammation, and lipid dysregulation.



Integrated Host–Microbe–Metabolic Framework

The integrated systems pharmacology model suggested that phytochemicals present in *Seeraka Rasayanam* may beneficially modulate gut microbial composition and microbial metabolite production, thereby regulating inflammatory and metabolic signaling pathways associated with dyslipidemia.

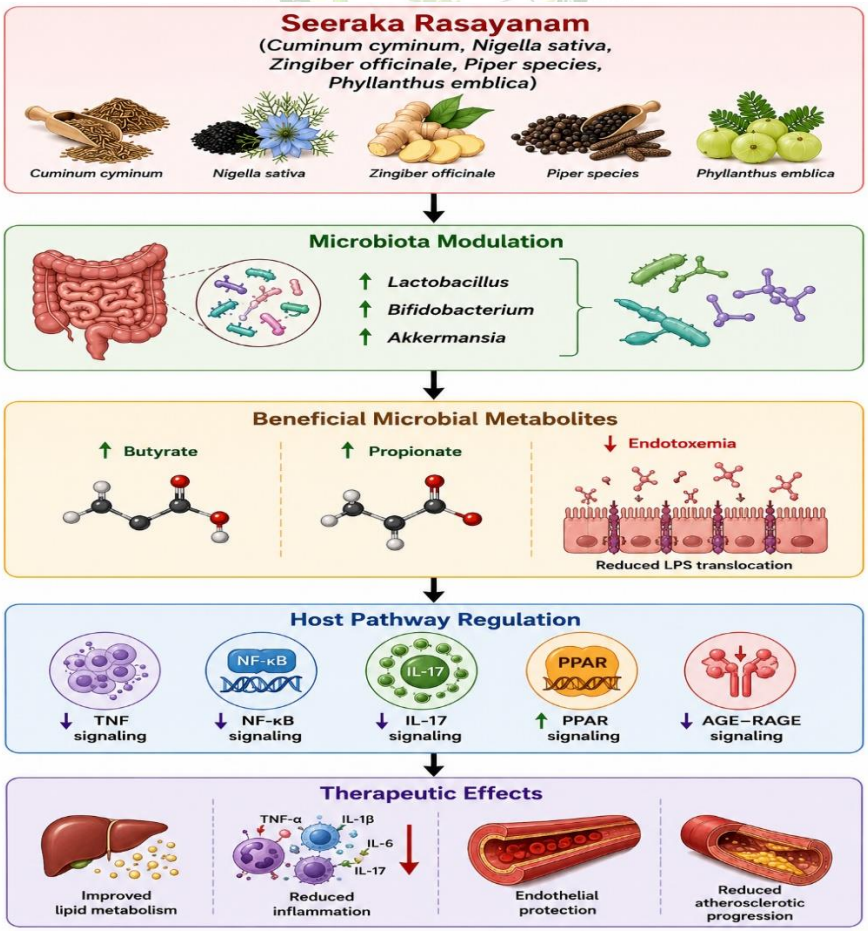
Figure 3: Phytochemical–Microbe–Metabolite–Pathway Cytoscape Network



The proposed framework indicates that *Seeraka Rasayanam* may exert therapeutic effects through:

- Enhancement of SCFA production,
- Reduction of endotoxemia,
- Suppression of inflammatory signaling,
- Improvement of endothelial function,
- Regulation of lipid metabolism.

Figure 4: Proposed gut microbiome-mediated mechanisms of *Seeraka Rasayanam* in dyslipidemia



DISCUSSION

The present study proposes a microbiome-centered systems pharmacology framework to explain the potential anti-dyslipidemic effects of *Seeraka Rasayanam*. Recent evidence indicates that gut microbiota plays a crucial role in lipid metabolism, chronic inflammation, endothelial dysfunction, and cardiovascular disease progression.

Gut dysbiosis contributes to increased intestinal permeability and translocation of lipopolysaccharides into systemic circulation, resulting in metabolic endotoxemia and activation of inflammatory pathways including TNF and NF-κB signaling. Chronic activation of these pathways contributes to oxidative stress, insulin resistance, endothelial dysfunction, and atherosclerotic progression.

Several phytochemicals identified in *Seeraka Rasayanam* possess reported microbiome-modulating properties. Piperine has been associated with enhancement of beneficial gut bacterial populations and improved intestinal barrier function. Thymoquinone exhibits anti-inflammatory and antioxidant effects and may contribute to suppression of dysbiosis-associated inflammatory responses.

Gingerol and gallic acid are associated with SCFA-producing bacteria including Faecalibacterium and Roseburia species. SCFAs exert beneficial effects through regulation of inflammatory signaling pathways, maintenance of gut barrier integrity, and improvement of lipid metabolism.

The PPAR signaling pathway identified in the present framework is closely associated with lipid homeostasis and fatty acid oxidation. SCFAs and microbial metabolites may activate PPAR-associated pathways, thereby contributing to metabolic regulation and reduction of lipid accumulation.

Similarly, the AGE–RAGE signaling pathway represents an important oxidative stress-associated mechanism implicated in endothelial dysfunction and cardiovascular complications. Antioxidant phytochemicals such as thymoquinone, gallic acid, gingerol, and plumbagin may potentially attenuate oxidative injury and vascular inflammation.

The IL-17 and NF-κB pathways are strongly associated with gut immune dysregulation and chronic inflammatory responses. Suppression of these pathways through microbiome-associated phytochemical interactions may contribute to improvement of dyslipidemia-associated inflammatory status.

Unlike conventional network pharmacology studies focusing solely on compound–target interactions, the present framework emphasizes the integration of phytochemicals, gut microbiota, microbial metabolites, and host inflammatory pathways. This host–microbe–metabolic interaction model provides a broader mechanistic understanding of Siddha formulations in metabolic disorders.

However, the present study is limited by its literature-based systems integration approach and requires further experimental validation through metagenomics, metabolomics, and in vivo investigations.

CONCLUSION

The present study proposes a microbiome-centered systems pharmacology framework for understanding the potential anti-dyslipidemic effects of *Seeraka Rasayanam*. The formulation contains multiple phytochemicals that may modulate gut microbial ecology, enhance beneficial microbial metabolites, suppress inflammatory signaling, and regulate lipid metabolic pathways.

The integrated phytochemical–microbe–metabolite–pathway axis suggests that Seeraka Rasayanam may exert therapeutic effects through regulation of gut microbiota-associated inflammatory and metabolic mechanisms implicated in dyslipidemia.

The findings provide a mechanistic basis for future experimental and clinical validation of Siddha formulations targeting the gut microbiome in metabolic disorders.

Future Perspectives

Future studies may include:

- Metagenomic profiling
- Microbiome sequencing
- Metabolomics analysis
- In vivo dyslipidemia models
- SCFA quantification
- Gut–liver axis validation studies

Integration of Siddha medicine with microbiome research may provide novel therapeutic approaches for metabolic and cardiovascular disorders.

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