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Deciphering the Multi-Target Molecular Mechanisms of *Rasnasaptakam Kashayam*: A Comprehensive Review of *in silico* and Network Pharmacology Potentials

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ABSTRACT

Background: *Rasnasaptakam Kashayam* is a classical *Ayurvedic* polyherbal decoction traditionally used to manage *Vata-Kapha* dominant musculoskeletal disorders, chronic joint pain, and inflammatory diseases. While its clinical efficacy is historically documented, the complex multi-component molecular mechanisms underlying its therapeutic action require modern systemic validation.
Objective: This review compiles and evaluates the current *in silico* data, molecular docking profiles, molecular dynamics simulations, network pharmacology pathways, and pharmacokinetics metrics of the formulation to map its systemic mechanism of action.
Data Source: Literature was gathered from digital databases including PubMed, Google Scholar, and localized traditional *Ayurvedic* drug repositories up to 2026.
Review Methods: Studies detailing computational validation, binding energies (ΔG), absorption, distribution, metabolism, and excretion parameters of the seven constituent herbs were synthesized. **Results:** Virtual high-throughput screenings confirm that core active compounds—such as quercetin, tinosporaside, boeravinone B, berberine, and ricinoleic acid—exhibit high negative binding affinities (ranging from -7.4 to -9.3 kcal/mol) against key human pro-inflammatory targets including cyclooxygenase-2, inducible nitric oxide synthase, tumor necrosis factor-alpha, nuclear factor-kappa B, and matrix metalloproteinase-9. Molecular dynamics trajectories over 100 nanoseconds validate the structural stability of these ligand-receptor configurations. Network pharmacology demonstrates a holistic, multi-pathway blockade that downregulates joint inflammation and preserves cartilage structural integrity.
Conclusion: *In silico* data provide solid, quantifiable proof that validates the multi-target, synergistic nature of *Rasnasaptakam Kashayam*, establishing a mechanistic framework for future human clinical evaluation.

Keywords: *Ayurveda*, *In silico*, Molecular docking, Network pharmacology, *Rasnasaptakam Kashayam*.

INTRODUCTION

Chronic musculoskeletal and degenerative joint disorders, including rheumatoid arthritis, osteoarthritis, lumbar spondylosis, and sciatica, represent severe clinical challenges globally [1]. In conventional medicine, therapeutic management is predominantly reliant on synthetic non-steroidal anti-inflammatory drugs (NSAIDs) and biological agents [1]. Though effective in providing short-term analgesic relief, prolonged use of these agents is frequently constrained by systemic risks, including gastrointestinal ulceration, nephrotoxicity, and adverse cardiovascular events.

Ayurveda offers a distinct paradigm through polyherbal matrices designed to exploit synergistic interactions among secondary plant metabolites. *Rasnasaptakam Kashayam*, a decoction formalized in classical texts like the *Sahasrayogam*, is traditionally indicated for treating *Amavata* (rheumatoid arthritis) and *Sandhigata Vata* (osteoarthritis) [4]. The formulation is processed from seven specific medicinal plants: *Pluchea lanceolata* (Oliver & Hiern) C.B. Clarke (*Rasna*), *Tinospora cordifolia* (Willd.) Hook. f. & Thomson (*Guduchi*), *Cassia fistula* L. (*Aragvadha*), *Cedrus deodara* (Roxb. ex D.Don) G.Don (*Devadaru*), *Tribulus terrestris* L. (*Gokshura*), *Ricinus communis* L. (*Eranda*), and *Boerhavia diffusa* L. (*Punarnava*) [4,5].

Modern pharmacological validation of complex *Ayurvedic* matrices requires a systems-biology strategy [6]. *In silico* computational methods, including molecular docking, molecular dynamics (MD) simulations, and network pharmacology, offer robust, high-throughput approaches to screen extensive plant chemical libraries [6,7]. This review systematically evaluates computational data to define the multi-target mechanics of *Rasnasaptakam Kashayam*

MATERIALS & METHODS

1. Methods for Data Extraction

A systematic digital search was executed across databases including PubMed, Google Scholar, and the Ayurveda Research Database. Keywords utilized included "*Rasnasaptakam Kashayam*", "molecular docking", "network pharmacology", "*Rasna Saptak Kwath*", and individual botanical names combined with computational target terms. Studies were filtered based on the inclusion of specific binding energy values (ΔG in kcal/mol), quantitative High-Performance Thin Layer Chromatography (HPTLC) marker screening, or formalized absorption, distribution, metabolism, and excretion (ADME) simulation data related directly to the constituent herbs [5].

2. Phytochemical Profiling and Standardization

To establish accurate ligand structural inputs for computational validation, chemical standardization must precede virtual screenings [8]. High-Performance Thin Layer Chromatography (HPTLC) fingerprinting serves as the primary analytical standard for checking polyherbal identity [8,9].

Densitometric scanning protocols performed at ultra-violet (UV) wavelengths of 254 nm and 366 nm isolate highly reproducible retention factor (\(R_{f}\)) sequences [9]. Utilizing standardized mobile phases, such as *Toluene: Ethyl Acetate: Formic Acid*, researchers have successfully quantified prominent polyherbal markers within the *Kashayam* matrix [8]. Chromatographic profiling consistently confirms the baseline presence of robust, anti-inflammatory polyphenols and flavonoids—most notably quercetin, gallic acid, and β-sitosterol [9]. These standardized markers provide the precise chemical structural data required for subsequent molecular docking scripts [7,9].

3. Virtual Screening and Molecular Docking Affinities

Molecular docking models simulate the precise geometric, spatial, and electrostatic interactions occurring between botanical ligands and active-site cavities of human disease receptors [7]. Thermodynamically, a lower negative binding energy (ΔG) indicates a more spontaneous, stable, and resilient ligand-receptor complex [10].

Computational screens identify significant binding affinities for several core compounds within the formulation against enzymes driving joint pathobiology [6,10].

Table 1: In Silico Binding Affinities and Target Profiles of Key Bioactive Ligands

Target Human Enzyme / Receptor	Bioactive Compound	Primary Botanical Source	Binding Energy (ΔG, kcal/mol)	Primary Structural Binding Mode / Interaction
Cyclooxygenase-2 (COX-2)	Quercetin	Omnipresent polyphenol matrix	-8.2 to -9.1	Hydrogen bonding at critical Arg120 and Tyr355 residue pockets [6,7]
Tumor Necrosis Factor-alpha (TNF-α)	Tinosporaside	Tinospora cordifolia (Guduchi)	-8.5 to -9.3	Strong hydrophobic mapping across the trimer subunit interface [10]
Nuclear Factor-kappa B (NF-kB p65)	Berberine	Tinospora cordifolia (Guduchi)	-8.8	Planar intercalation within active DNA-binding loops [6,11]
Matrix Metalloproteinase-9 (MMP-9)	Boeravinone B	Boerhavia diffusa (Punarnava)	-7.6 to -8.1	Structural coordination directly with the active-site catalytic Zinc ion (Zn^{2+}) [10,12]
Inducible Nitric Oxide Synthase (iNOS)	Ricinoleic acid	Ricinus communis (Eranda)	-7.4 to -7.9	Hydrophobic mapping within the oxygenase catalytic domain [12]

3.1 Molecular Dynamics (MD) Validation

To ensure that these static docking snapshots translate accurately to fluid biological environments, long-range molecular dynamics simulations (extending to 100 nanoseconds or greater) are applied [7]. The Root-Mean-Square Deviation (RMSD) profiles for target proteins such as COX-2 and TNF-α complexed with quercetin or tinosporaside show minimal spatial deviation (fluctuations remaining below 2.0 Å) [10]. This confirms that the therapeutic molecules maintain highly stable binding configurations without dissociating over time under simulated physical parameters [7,10].

4. Network Pharmacology and Pathway Analysis

While standard single-molecule drugs function through linear pathways, the polyherbal synergy of *Rasnasaptakam Kashayam* operates via a broad, network-based pathway topology [11]. Interacting target profiles assembled via bio-computational databases confirm a coordinated therapeutic mechanism [11,13]:

- **Inhibition of the Genomic Inflammatory Switch:** Network mapping reveals that *tinosporaside* and *berberine* work upstream to inhibit IκB kinase (IKK) core phosphorylation [11]. This structural block prevents the transcription factor NF-kB from translocating into the host cell nucleus, halting the expression of cascading pro-inflammatory interleukins (IL-1β, IL-6) and systemic cytokines [6,11].
- **Preservation of Joint Matrix Architecture:** The downstream structural degradation of joint tissue in osteoarthritic changes is mitigated by the action of *boeravinone B* [12]. Computational network nodes place this ligand at the center of Matrix Metalloproteinase regulation, suppressing MMP-3 and MMP-9 production to protect joint cartilage collagen from enzymatic destruction [10,12].

5. Pharmacokinetic Profiling (ADME) and Drug-Likeness

A molecular structure can only be effective in the body if it displays viable pharmacokinetic traits [13]. Computational tools applying Lipinski's Rule of Five

screen the drug-likeness of the formulation's phytochemicals [13,14].

- **Lipinski Compliance:** Upwards of 85% of identified polyphenols, lignans, and sterols extracted from the seven raw materials align with standard structural rules (molecular weight <500 Da, Lipophilicity LogP <5, hydrogen bond donors <5, and hydrogen bond acceptors <10) [13].
- **Gastrointestinal (GI) Absorption & Toxicity:** Virtual ADME configurations predict excellent human intestinal absorption percentages for both *quercetin* and *ricinoleic acid* [14]. Furthermore, ProTox-II *in silico* profiles show no mutagenic, carcinogenic, or immunotoxic risks [13,14].
- **Blood-Brain Barrier (BBB) Permeability:** Simulations show very low blood-brain barrier penetration for these compounds [14]. This restricts the formula's activity to peripheral inflamed tissues, eliminating central nervous system side effects such as drowsiness or dizziness [13].

DISCUSSION

The quantitative data generated across these computational studies offer a clear scientific bridge connecting classical *Ayurvedic* therapeutics with modern molecular biology. Traditional *Ayurvedic* philosophy dictates that *Rasnasaptakam Kashayam* works through its *Vata-Hara* (anti-neurological pain) and *Shothahara* (anti-edematous/anti-inflammatory) attributes [4]. The *in-silico* findings translate these concepts directly into measurable data: *Vata-Hara* actions correspond to downregulating COX-2 and prostaglandin production, while *Shothahara* activity matches the inhibition of TNF-α and iNOS pathways [6,10,12].

Unlike isolated single compounds, which can trigger cellular resistance or bypass loops, the broad target network of *Rasnasaptakam Kashayam* ensures a stable therapeutic response [11]. If an inflammatory process tries to bypass COX-2 inhibition, the concurrent down-regulation of the NF-kB switch by *Guduchi* compounds blocks secondary inflammatory pathways [6,11]. Standardizing the manufacturing process via HPTLC ensures these bio-effective markers remain consistent across separate production batches [8,9].

CONCLUSION

This review synthesizes the *in silico* molecular profile of *Rasnasaptakam Kashayam*. The compilation of strong docking scores, persistent molecular dynamics trajectories, and interconnected network pharmacology pathways validates its traditional clinical application. By acting across multiple biological systems, it safely manages pain and inflammation while protecting joint cartilage. These computational insights provide the concrete pharmacological benchmarks needed to design future human clinical trials

Declaration by Authors

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