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A COMPREHENSIVE AYURVEDA CLASSICAL, PHARMACOLOGICAL AND CLINICAL REVIEW OF ANTI-FUNGAL AND IMMUNOMODULATORY EFFECT OF DVITIYA EDAGAJADI LEPA AND ARAGVADHADI KASHAYA IN THE MANAGEMENT OF DADRU KUSHTA (TINEA CORPORIS)

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ABSTRACT

Background: Dadru Kushta, described in Ayurvedic classical texts as a chronic skin disorder with manifestations of itching (kandu), redness (raga), pustules (pidaka) and raised circular patches (udgatam mandala), closely correlates with the modern dermatological entity of Tinea corporis (ringworm of the body) — a dermatophytic fungal infection of significant global public health importance.[1,2] **Objective:** This review critically evaluates the Ayurvedic classical textual basis, phytochemical constituents, pharmacokinetic and pharmacodynamic profiles, pharmacological activities, and available clinical evidence pertaining to Dvitiya Edagajadi Lepa and Aragvadhadi Kashaya, compared with Prathama Edagajadi Lepa and Aragvadhadi Kashaya, as formulated in Chakradatta, in the management of Dadru Kushta with special reference to Tinea corporis. **Methods:** A comprehensive literature search was conducted across PubMed, DHARA, AYUSH Research Portal, classical Ayurvedic texts (Charaka Samhita, Sushruta Samhita, Ashtanga Hrudaya, Ashtanga Sangraha, Chakradatta, Sharangadhara Samhita, Bhavaprakasha, Madhava Nidana, Kashyapa Samhita, and Bhela Samhita), and contemporary pharmacological journals. Articles relevant

to the constituent drugs, their phytochemistry, antifungal properties, and clinical trials were reviewed and synthesized. **Results:** Dvitiya Edagajadi Lepa contains additional ingredients — Pippali (*Piper longum* Linn), Tila (*Sesamum indicum* Linn), and Lavana traya — compared to Prathama Edagajadi Lepa, conferring enhanced antifungal, anti-inflammatory, and skin-penetration-enhancing properties through piperine, sesamin, and sodium chloride respectively.[11,12] Aragvadhadi Kashaya, comprising Aragvadha, Pippali mula, Musta, Katuka, and Haritaki, provides synergistic kusghtaghna, krimighna, and kandughna effects internally.[9] **Conclusion:** Dvitiya Edagajadi Lepa, by virtue of its additional phytochemical constituents, demonstrates theoretically superior antifungal, anti-inflammatory, and bio-enhancing properties over Prathama Edagajadi Lepa for management of Dadru Kushta/Tinea corporis. Controlled clinical trials are warranted to validate these findings.

KEYWORDS: Dadru Kushta, Tinea corporis, Dvitiya Edagajadi Lepa, Prathama Edagajadi Lepa, Aragvadhadi Kashaya, Piperine, Dermatophytosis, Kushtaghna.

1. INTRODUCTION

The human skin, comprising an area of approximately 2 m² and weighing about 4 kg, represents the largest organ of the human body and serves as the primary physical defence barrier against environmental stimuli, pathogens, and chemical insults.[1,2] Its complex multilayered architecture, constituted by the epidermis, dermis, and hypodermis, enables a spectrum of functions including thermoregulation, sensory perception, immunological surveillance, and metabolic activity.[2] Fungal infections of the skin represent a major global burden of morbidity. Epidemiological data indicate that approximately 6.5 million invasive fungal infections occur annually worldwide, contributing to an estimated 3.8 million deaths.[3] Dermatophytosis — the superficial mycosis caused by keratinophilic fungi of the genera *Trichophyton*, *Microsporum*, and *Epidermophyton* — is among the most prevalent, affecting approximately 20–25% of the global population at any given time.[4] Tinea corporis (ringworm of the body) specifically accounts for a substantial proportion of dermatophytic consultations. In India, the prevalence of dermatophytosis ranges from 36.6% to 78.4% across various geographic zones, and approximately 5 in every 1,000 Indians are affected by tinea infections.[5] Contemporary management of Tinea corporis employs topical azole antifungals (clotrimazole, miconazole) as first-line therapy, with systemic agents such as itraconazole and terbinafine reserved for recalcitrant, widespread, or follicular disease.[6] However, long-term systemic azole use carries well-documented risks including

hepatotoxicity, alterations in endocrine hormonal balance (particularly estrogen), severe hypersensitivity reactions including Stevens-Johnson syndrome, and the emergence of antifungal drug resistance.[7] These limitations have catalysed renewed interest in traditional botanical therapies, particularly those rooted in the time-tested Ayurvedic pharmacopoeia.

In Ayurvedic medicine, Dadru Kushta is classified as a Kshudrakushta (minor skin disease) by Acharya Charaka[14] and as a Mahakushta by Acharya Sushruta,[18] reflecting nuanced differences in pathological severity. Its aetiopathogenesis involves the vitiation of Kapha and Pitta doshas, leading to the characteristic manifestations of kandu (pruritus), raga (erythema), pidaka (papulo-pustular eruptions), and udgatam mandala (raised annular patches with centrifugal spread) — features that closely map onto the clinical presentation of Tinea corporis.[14,22] Chakradatta, one of the authoritative texts of Ayurvedic clinical medicine authored by Acharya Chakrapanidatta (11th century CE), describes both Prathama Edagajadi Lepa and Dvitiya Edagajadi Lepa for the external management of Dadru Kushta, alongside Aragvadhadi Kashaya as an internal shamana (pacifying) formulation.[8,9,10] While Prathama Edagajadi Lepa contains five ingredients, Dvitiya Edagajadi Lepa includes three additional constituents — Pippali, Tila, and Lavana traya — potentially conferring enhanced therapeutic efficacy through complementary phytochemical mechanisms.[8,10] This review systematically synthesises the classical Ayurvedic textual basis, phytochemical profiles, pharmacokinetic and pharmacodynamic properties, pharmacological activities, and available clinical evidence pertaining to both formulations and their constituent drugs, with the aim of providing a scholarly foundation for ongoing and future clinical research.

2. DADRU KUSHTA: CLASSICAL AYURVEDIC PERSPECTIVE

2.1 Etymological and Nosological Classification

The term 'Dadru' is derived from the Sanskrit root referring to a skin condition characterised by spreading, circinate lesions. Classical Ayurvedic nosology recognises two parallel classification systems for Kushta (skin diseases): the enumeration by Charaka placing Dadru among 18 Kshudrakushtas,[14] and that of Sushruta classifying Dadru under Mahakushta.[18] Both schools, however, agree upon its fundamental doshic aetiology as a Kapha-Pittaja condition, with Pitta predominance explaining the erythematous, spreading, and burning quality of lesions, and Kapha predominance accounting for the pruritus, moistness, and chronicity.

2.2 Description in Charaka Samhita

Acharya Charaka includes Dadru among diseases of Rakta (blood tissue) in the Sutrasthana (Chapter 28), establishing a haematogenous pathological dimension to its aetiopathogenesis.[13] The Nidanasthana (Chapter 5, Shloka 4) describes the cardinal symptoms of Dadru as kandu (itching), raga (redness), and pidaka (papules/pustules), attributing the condition to excessive intake of incompatible, liquid, unctuous, and heavy dietary substances along with unhygienic living practices.[14]

2.3 Description in Sushruta Samhita

Acharya Sushruta elevates the significance of Kushta by classifying it among the Mahagada (major diseases) in the Sutrasthana (Chapter 33, Shloka 4),[15] and discusses its Papajanya (karmic) dimension in the Nidanasthana (Chapter 5, Shloka 30).[16] His Chikitsasthana (Chapter 9) provides comprehensive guidance on pathya-apathya (dietary and lifestyle regimen), emphasising long-term management principles.[17] Dadru is characterised by Sushruta as displaying tamravarna (copper-red colouration) and atasipushpavarna (linseed flower-coloured) lesions — vivid descriptions aligning with the erythematous-annular plaques of Tinea corporis.[18]

2.4 Description in Ashtanga Hrudaya and Ashtanga Sangraha

Acharya Laghu Vagbhata in Ashtanga Hrudaya (Nidanasthana, Chapter 14) includes krimi (microorganisms/parasites) among the nidanas (causative factors) of Kushta,[19] a remarkably prescient observation anticipating the modern understanding of fungal aetiology. He further elaborates upon the progressive tissue involvement from loma (hair follicles) to tarunaasthi (cartilage) when the disease remains untreated,[20] and follows Sushruta's classification with additional clarifications on Mahakushta and Kshudrakushta management principles.[21] Dadru is described with symptoms of kandu, pidaka, and Kapha-Pitta predominance.[22] Vriddha Vagbhata in Ashtanga Sangraha (Nidanasthana, Chapter 14) confirms the Kapha-Pittaja classification of Dadru[23] and notes that vata-kaphaja varieties of Kushta are relatively sukhasadhya (easily curable), providing important prognostic guidance.[24]

2.5 Description in Other Classical Texts

Sharangadhara Samhita (Madhyama Khanda, Chapter 2) contributes new Kushtaghna (anti-skin disease) formulations to the therapeutic armamentarium[25,26] while Madhava Nidana and Yogaratnakara echo Sushruta's symptom descriptions for Dadru.[27,28] Bhavaprakasha (Madhyama Khanda, Chapter 54) synthesises the sadhya-asadhyata (curability criteria) from

Sushruta.[29] Bhela Samhita enumerates Dadru Kushta in both its Nidanasthana and Chikitsasthana,[30] while Kashyapa Samhita provides distinct clinical descriptions including ruksha (dry), kandu (itchy), daaha (burning), and sraava (discharge) as presenting features.[31]

3. MODERN CORRELATE: TINEA CORPORIS

Tinea corporis (ringworm of the body) is a superficial dermatophytic infection of the glabrous skin of the trunk, legs, arms, and neck, sparing the palms, soles, and groin. It is most commonly caused by *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Microsporum canis*.[4] The classic presentation is an erythematous annular plaque with a raised, scaly, advancing border and central clearing — directly analogous to the udgatam mandala (elevated circular patches) and raga-kandu-pidaka triad of Dadru Kushta.[5] The global prevalence of dermatophytosis is estimated at approximately 20–25% of the world population, making it the most common infectious disease of the skin.[4] In India, particularly in tropical and subtropical regions with humid climate, overcrowding, and poor hygiene infrastructure, the prevalence is markedly higher, with dermatophytes isolated in 36.6–78.4% of cases presenting to dermatology clinics.[5] The condition affects individuals of all ages but demonstrates a peak prevalence of approximately 20% among persons aged 40–60 years, with an overall community prevalence of approximately 2% among young adults.[4] Standard contemporary management involves topical imidazoles (clotrimazole, miconazole, ketoconazole) applied twice daily for 2–4 weeks, or topical allylamines (terbinafine) for 1–2 weeks.[6] Systemic therapy with itraconazole or terbinafine is warranted for extensive, inflammatory, or folliculotropic disease.[6] However, the emergence of pan-azole-resistant *T. indotineae* in the Indian subcontinent represents a critical contemporary challenge to conventional therapy, underscoring the urgency of developing alternative antifungal strategies.[7]

4. FORMULATION REVIEW: PRATHAMA EDAGAJADI LEPA

4.1 Classical Source and Composition

Prathama Edagajadi Lepa is described in Chakradatta (Chapter 50, Shloka 36) by Acharya Chakrapanidatta for the management of Dadru Kushta.[10] The formulation comprises five drugs: Edagaja (*Cassia tora* Linn, Chakramarda), Kushta (*Saussurea lappa* C.B Clarke), Saindava (rock salt), Sarsapa (*Brassica campestris* Linn), and Vidanga (*Embelia ribes* Burn. F). All drugs are powdered separately, sieved, and the resultant fine powder is applied externally using sour gruel (Kanji/amla dravya) as the anupana (vehicle).[34]

4.2 Dravyaguna Analysis of Individual Ingredients

4.2.1 Edagaja (*Cassia tora* Linn / **Chakramarda):** Edagaja is the principal drug of both lepas, endowed with Kapha-Vata shamaka properties and Kushtaghna, Kandughna, and Dadrughna karma (actions).[32] Pharmacologically, seed extracts of *Cassia tora* demonstrate significant antifungal activity against dermatophytes including *T. rubrum* and *T. mentagrophytes*, attributed to chrysophanol, physcion, emodin, and other anthraquinone derivatives that disrupt fungal cell membrane integrity and inhibit ergosterol biosynthesis.[34]

4.2.2 Kushta (*Saussurea lappa* C.B Clarke): Kushta root exhibits Kapha-Vata shamaka properties with Kushtaghna and Rasayana karma.[32] Its principal bioactive constituents — costunolide, dehydrocostus lactone, and cynaropicrin — demonstrate broad-spectrum antimicrobial and anti-inflammatory activities. Sesquiterpene lactones in Kushta have been documented to inhibit NF-κB-mediated pro-inflammatory signalling pathways, reducing erythema and pruritus.[34]

4.2.3 Sarsapa (*Brassica campestris* Linn**):** Sarsapa exhibits Kapha-Vata shamaka action with documented Kandughna (anti-pruritic) and Kushtaghna properties.[32] Allyl isothiocyanate, the principal volatile constituent of mustard seeds, exhibits potent antifungal activity through membrane disruption and inhibition of fungal hyphal growth. Erucic acid and other fatty acids in Sarsapa may enhance drug penetration through the stratum corneum when formulated as a lepa.[34]

4.2.4 Vidanga (*Embelia ribes* Burn. F**):** Vidanga possesses Kapha-Vata shamaka action with Kushtaghna and Krimighna (anti-parasitic/antimicrobial) karma — particularly significant in the context of fungal aetiology.[32] Embelin (2,5-dihydroxy-3-undecyl-1,4-benzoquinone), the principal active constituent of Vidanga, exhibits documented antifungal activity. Studies have demonstrated embelin's ability to inhibit dermatophyte growth through disruption of mitochondrial electron transport and induction of oxidative stress within fungal cells.[34]

4.2.5 Saindava (Rock Salt): Saindava (Tridoshahara) exerts its therapeutic role in lepa preparations through mild keratolytic activity, facilitating penetration of active phytoconstituents across the stratum corneum, and through osmotic disruption of the fungal cell environment. Its hygroscopic properties may also contribute to drying of moist, weeping lesions.[34]

5. FORMULATION REVIEW: DVITIYA EDAGAJADI LEPA

5.1 Classical Source and Composition

Dvitiya Edagajadi Lepa is described in Chakradatta (Chapter 50, Shloka 39) and constitutes the investigational formulation under clinical evaluation.[8] It contains eight ingredients: Edagaja (*Cassia tora* Linn*)*, Tila (*Sesamum indicum* Linn), Sarsapa (*Brassica campestris* Linn*)*, Kushta (*Saussurea lappa* C.B Clarke*)*, Pippali (*Piper longum* Linn), and Lavana traya (Saindava, Vida/Vida lavana, and Souvarchala lavana). The method of preparation and application is identical to Prathama Edagajadi Lepa, employing sour gruel as the vehicle.[33]

Comparative analysis reveals that Dvitiya Edagajadi Lepa incorporates three additional constituents — Tila, Pippali, and Lavana traya (three salts) — not present in Prathama Edagajadi Lepa. The theoretical basis for enhanced efficacy rests upon the complementary and synergistic pharmacological properties of these additional ingredients.

5.2.1 Pippali (*Piper longum* Linn**):** Pippali is classified as Kapha-Vata shamaka with Kandughna and Kushtaghna properties in Dravyaguna.[32] Its principal bioactive alkaloid, piperine (1-piperoyl piperidine), has been extensively investigated. Tripathi et al., in a comprehensive review published in the National Library of Medicine (2022), documented that piperine demonstrates significant anti-inflammatory activity through inhibition of COX-2 and 5-LOX enzymes, antioxidant activity via free radical scavenging, and direct antifungal properties against both filamentous fungi and yeasts.[11] Crucially, piperine acts as a bioavailability enhancer (bioperine effect) — documented to increase the oral bioavailability of co-administered drugs by 30–200% through inhibition of intestinal and hepatic cytochrome P450 (CYP3A4) isoenzymes and P-glycoprotein efflux pumps.[11] When applied topically in lepa formulations, piperine's role as a penetration enhancer may significantly augment transdermal delivery of co-formulated antifungal constituents across the stratum corneum — a property with substantial implications for topical Ayurvedic dermatological therapeutics.

5.2.2 Tila (*Sesamum indicum* Linn**):** Tila is accorded Vatahara, Twachya (skin-benefiting), and Rasayana properties in classical Dravyaguna texts.[32] A study by Ogawa et al. (2013) demonstrated that edible sesame oil possesses significant inhibitory activity against clinical isolates of *Candida albicans*, with the antifungal effect attributed to the lignan sesamin (3,4-methylenedioxy phenyl compound) and its metabolites.[12] Sesamin has been shown to inhibit fungal cytochrome P450 enzymes required for ergosterol biosynthesis — the same

mechanism exploited by conventional azole antifungals — through competitive binding to the CYP51 (lanosterol 14α-demethylase) enzyme. Furthermore, sesamin exhibits documented anti-inflammatory activity through suppression of NF-κB and MAP kinase signalling cascades, potentially attenuating the inflammatory response in Dadru lesions.[12] Tila seeds also contain abundant oleic acid and linoleic acid, which serve as excellent emollient bases in topical formulations, enhancing stratum corneum hydration, restoring the disrupted skin lipid barrier, and improving drug residence time within the target tissue.[12]

5.2.3 Lavana Traya (Three Salts — Saindava, Vida, Souvarchala): The inclusion of a triad of mineral salts represents a distinctive pharmacological feature of Dvitiya Edagajadi Lepa. Beyond the basic Tridoshahara properties attributed to Saindava, the Vida lavana (ammonium chloride) contributes keratolytic properties facilitating desquamation of hyperkeratotic fungal-infected stratum corneum, enhancing penetration of antifungal constituents.[33] Souvarchala lavana (black salt, containing trace sulphur compounds) may contribute antimicrobial and anti-inflammatory properties. The collective osmotic, keratolytic, and pH-modifying effects of the three-salt combination create a hostile microenvironment for dermatophyte survival within the stratum corneum while simultaneously enhancing percutaneous absorption of bioactive phytoconstituents.[33]

6. FORMULATION REVIEW: ARAGVADHADI KASHAYA

6.1 Classical Source and Composition

Aragvadhadi Kashaya is described in Chakradatta (Chapter 1, Shloka 141) as an internal shamana (pacifying) formulation for Kushta management.[9] It comprises five drugs taken in equal proportions: Aragvadha leaves (*Cassia fistula* Linn), Pippali mula root (*Piper longum* Linn), Musta tubers (*Cyperus rotundus* Linn), Katuka root (*Picrorhiza kurroa* Royle ex Benth), and Haritaki fruit (*Terminalia chebula* Retz). The preparation involves decoction — the coarse drug powder is boiled with four parts of water, reduced to one-quarter volume (kwatha), filtered and preserved with 0.01% sodium benzoate.[35,36]

6.2 Pharmacological Analysis of Aragvadhadi Kashaya Ingredients

6.2.1 Aragvadha (*Cassia fistula* Linn**):** Aragvadha, the eponymous drug of the formulation, exhibits Kapha-Pitta shamana action with principal Kushtaghna karma,[35] establishing it as the primary therapeutic agent. Its bioactive constituents include anthraquinone glycosides (sennoside A and B, rhein, aloe-emodin), fistulic acid, tannins, and flavonoids. Clinical and experimental studies have documented broad-spectrum antibacterial and antifungal activities

of *Cassia fistula* extracts. Aqueous and ethanolic leaf extracts demonstrate significant inhibition of dermatophyte growth in vitro, while seed extracts exhibit MIC values against *T. rubrum* comparable to standard topical azoles. The Kapha-Pitta shamana property directly addresses the fundamental doshic pathology of Dadru Kushta.[35]

6.2.2 Pippali Mula (Root of *Piper longum* Linn**):** Pippali mula shares the principal phytochemical constituents of the fruit, including piperine and piperlongumine, with documented Krimighna (antimicrobial/antiparasitic) and Kapha-Vata hara properties.[32] Its inclusion in Aragvadhadi Kashaya as an internal formulation allows systemic delivery of piperine, potentially enhancing bioavailability of co-administered drugs and providing systemic anti-inflammatory effects through COX and LOX pathway inhibition — addressing the systemic dimensions of Dadru Kushta aetiopathogenesis including Rakta dushti (blood tissue vitiation).[11]

6.2.3 Musta (*Cyperus rotundus* Linn**):** Musta, a Kapha-Pitta shamaka drug, contains sesquiterpenes (cyperene, cyperol, isocyperol), flavonoids (quercetin, kaempferol), and alkaloids with documented anti-inflammatory, antioxidant, and antimicrobial activities.[35] The Krimighna karma of Musta encompasses antifungal properties — ethanol extracts of *C. rotundus* rhizomes have been documented to inhibit *T. rubrum* and *T. mentagrophytes* growth in vitro. Its role in Aragvadhadi Kashaya encompasses addressing the Pitta-kaphaja doshic dysregulation underlying Dadru Kushta through systemic anti-inflammatory mechanisms.

6.2.4 Katuka (*Picrorhiza kurroa* Royle ex Benth**):** Katuka (Kapha-Pitta shamaka) contains iridoid glycosides (kutkin = picroside I + kutkoside), which are among the most potent hepatoprotective compounds in Ayurvedic pharmacopoeia.[35] The Kandughna and Kushtaghna karma of Katuka in Aragvadhadi Kashaya serves the dual purpose of liver protection (critical in the context of long-term use and potential hepatotoxicity of concomitant treatments) and systemic immune modulation. Kutkin has been shown to enhance cell-mediated immunity through augmentation of macrophage and natural killer cell activity, potentially restoring the compromised cutaneous immune surveillance in chronic fungal infections.[35]

6.2.5 Haritaki (*Terminalia chebula* Retz**):** Haritaki, described as the 'king of medicines' in Ayurvedic literature, is a Tridoshahara rasayana drug with Kandughna and Krimighna properties.[32] It contains gallic acid, ellagic acid, chebulinic acid, chebulagic acid, and

numerous other hydrolysable tannins. These polyphenolic constituents have demonstrated direct antifungal activity against dermatophytes through multiple mechanisms: disruption of fungal cell wall synthesis, inhibition of fungal protease enzymes critical for keratinolysis (the key virulence factor of dermatophytes), and interference with ergosterol biosynthesis. Haritaki additionally promotes wound healing, reduces post-inflammatory hyperpigmentation, and restores normal skin barrier function through stimulation of type I collagen synthesis in fibroblasts.[32]

7. PHARMACOKINETIC CONSIDERATIONS

7.1 Topical Formulations (Lepa)

The pharmacokinetics of topical Ayurvedic lepa formulations are governed by the physicochemical properties of constituent drugs, the nature of the vehicle, and the physiological characteristics of the skin at the application site. The use of sour gruel (kanji, pH approximately 3.5–4.0) as the application vehicle in both Edagajadi lepas serves multiple pharmacokinetically relevant functions: the acidic pH maintains the integrity of acid-stable bioactive constituents, the mild acidity may augment stratum corneum permeability through reversible alteration of lipid bilayer organisation, and the lactic acid content of fermented gruel acts as a natural keratolytic facilitating drug penetration.[33] The bioavailability of topically applied drugs depends critically on partition coefficients (log P), molecular weight (<500 Da for optimal stratum corneum penetration), and degree of ionisation at skin surface pH. The principal anthraquinones of Edagaja (emodin, physcion) possess log P values of 1.5–2.5 and molecular weights in the range 270–284 Da, conferring favourable transepidermal penetration characteristics. Piperine (log P 1.66, MW 285 Da) and sesamin (log P 3.58, MW 354 Da) likewise exhibit physicochemical profiles amenable to transdermal delivery.[11,12] The inclusion of Tila oil (sesame oil) as a constituent of Dvitiya Edagajadi Lepa provides an endogenous lipid carrier system. Sesame oil, rich in oleic acid (C18:1) and linoleic acid (C18:2), functions as a penetration enhancer through reversible alteration of intercellular lipid organisation in the stratum corneum — increasing drug flux across the skin barrier by 2–10 fold compared to aqueous formulations.[12] Piperine's role as a penetration enhancer is further supported by documented inhibition of P-glycoprotein-mediated drug efflux at epidermal barriers.[11]

7.2 Internal Administration (Kashaya)

Aragvadhadi Kashaya, administered as an aqueous decoction at a dose of 20 mL twice daily (approximately ½ pala) before food, represents the oral systemic limb of the therapeutic strategy. The aqueous preparation maximises extraction of water-soluble constituents including glycosides, tannins, and alkaloid salts while minimising lipid-soluble pro-drug conversion.[36,37] Following oral administration, the principal bioactive constituents of Aragvadhadi Kashaya undergo first-pass hepatic metabolism. The pharmacokinetic synergy of piperine, derived from Pippali mula within the formulation, is particularly noteworthy: piperine inhibits CYP3A4-mediated hepatic first-pass metabolism and P-glycoprotein-mediated intestinal efflux, potentially augmenting the oral bioavailability of co-administered constituents including ellagic acid from Haritaki and polyphenolic constituents from Aragvadha and Katuka.[11]

8. PHARMACODYNAMIC MECHANISMS AND SYNERGY

8.1 Antifungal Mechanisms

The constituent drugs of both formulations target multiple steps in dermatophyte pathogenesis through complementary mechanisms:p[11,12,34,35]

Ergosterol biosynthesis inhibition: Anthraquinones from Edagaja and sesamin from Tila target fungal CYP51 (lanosterol 14α-demethylase), disrupting ergosterol biosynthesis — the principal antifungal mechanism shared with conventional azole antifungals. This mechanism is reinforced synergistically in Dvitiya Edagajadi Lepa by the additional sesamin content.[12,34]

Cell membrane disruption: Allyl isothiocyanate from Sarsapa and embelin from Vidanga disrupt dermatophyte cell membrane integrity through direct lipophilic membrane insertion, increasing permeability and inducing ion leakage. Piperine may potentiate this effect through membrane fluidisation.[11]

Keratinase inhibition: Tannins (gallic acid, ellagic acid) from Haritaki in Aragvadhadi Kashaya inhibit keratinolytic protease enzymes essential for dermatophyte invasion of cornified epithelium, addressing the pathogen's primary virulence mechanism at source.[35]

Immune modulation: Kutkin from Katuka and gallic acid from Haritaki stimulate cell-mediated immunity, restoring defective cutaneous immune surveillance that predisposes to chronic dermatophytic infection.[35]

8.2 Anti-inflammatory and Antipruritic Mechanisms

Pruritus (kandu) is the dominant symptom governing quality-of-life impairment in Dadru Kushta/Tinea corporis. The anti-pruritic pharmacodynamics of the formulations operate through multiple pathways: piperine-mediated COX-2 and 5-LOX inhibition reduces prostaglandin E2 and leukotriene B4 release, directly attenuating the arachidonic acid cascade driving pruritus and erythema.[11] Sesamin-mediated NF-κB suppression reduces downstream cytokine (IL-1β, TNF-α, IL-6) production, attenuating the inflammatory infiltrate responsible for raga (erythema) and oedema.[12] Costunolide from Kushta and sennosides from Aragvadha/Edagaja further contribute to anti-inflammatory effects through complementary signalling pathway modulation.

8.3 Skin Barrier Restoration (Twachya and Rasayana Effects)

Tila (sesame oil components) and Kushta exert documented Twachya (skin-nurturing) and Rasayana (regenerative/adaptogenic) effects. The fatty acid composition of sesame oil replenishes intercellular stratum corneum lipids depleted by dermatophyte-mediated ceramidase activity, restoring the impaired epidermal lipid barrier — a critical factor in preventing disease recurrence.[12] Haritaki promotes dermal collagen synthesis and re-epithelialisation through fibroblast growth factor (FGF) signalling pathway stimulation, contributing to complete resolution of lesions and prevention of post-inflammatory sequelae.[35]

9. CLINICAL EVIDENCE

9.1 Studies on Edagajadi Lepa Formulations

A randomised comparative clinical study at DGM Ayurvedic Medical College, Gadag (2017), by Dr. Kusum Mahajan evaluated Moolakabeejadi Lepa versus Durvadilepa in Dadru Kushta with reference to Tinea corporis, establishing the methodological template for controlled comparative trials in this domain.[39,40] The study demonstrated statistically significant reduction in subjective parameters (kandu, raga, pidaka) and objective parameters (lesion area, KOH examination positivity) following topical lepa therapy over a structured 45-day treatment course — directly informing the design parameters for the Edagajadi Lepa comparative trial. An open label single arm study at SDM Ayurvedic Medical College, Udupi

(2017), by Dr. Shrividya evaluated topical Chakramarda beeja taila (Cassia tora seed oil) in Dadru with reference to Tinea corporis/cruris. The demonstrated efficacy of Cassia tora-based preparations provides direct clinical validation for the Edagaja (Chakramarda) component as the principal therapeutic drug of both Edagajadi lepa formulations.[39]

9.2 Studies on Related Formulations

A clinical observation study at Government Ayurvedic Medical College, Mysore (2011), by Dr. Madhu evaluated the combined effect of Vidangadi yoga, Darviguduchyadi kashaya, and Durvadilepa in Dadru with respect to Tinea — demonstrating the principle of combined internal kashaya and external lepa therapy, which underpins the rationale of the current Edagajadi Lepa-Aragvadhadi Kashaya combination protocol.[39] A study at SDM Ayurvedic Medical College, Hassan (2015), by Dr. Rakesh H.R. evaluated Manibhadra guda with siddharthaka snana choorna lepa in Dadru Kushta (Tinea corporis), further establishing the evidence base for compound Ayurvedic formulations in dermatophytosis.[39] A comparative clinical study at Government Ayurvedic Medical College, Mysore (2016), by Dr. Viney Deep Singh Guleria on Dadru vidravan malahara yoga and Suddha gandaka in Dadru with reference to fungal dermatophytes confirmed the superiority of combination antifungal formulations over single-drug preparations in producing sustained clinical remission.[40]

9.3 Evidence for Piperine as Bioavailability Enhancer

Tripathi et al.'s systematic review in the National Library of Medicine (2022) synthesised clinical trial evidence establishing piperine as a clinically significant bioavailability enhancer. Multiple Phase II–III clinical trials have demonstrated piperine's ability to increase bioavailability of co-administered drugs including curcumin (2000% increase), resveratrol, and beta-carotene. The documented anti-hepatotoxic and antioxidant effects of piperine in clinical trials are particularly relevant given the hepatotoxicity risk profile of conventional antifungal therapy with azoles.[11]

9.4 Dermatophytosis Severity Score (DSS) as Validated Assessment Tool

Bhat et al. (Wiley Online Library, Mycoses, Volume 66, Issue 4, 2022) developed and validated the Dermatophytosis Severity Score (DSS), incorporating body surface area involvement across anatomical regions (head and neck, trunk, upper limbs, lower limbs), intensity of clinical features (erythema, raised border, scaling), and nail involvement.[41,42] The calculated total score formula $0.1\times Area(H)\times(Eh+Rh+Sh)+0.2\times Area(UL)\times(Eu+Ru+Su)+0.3\times Area(T)\times(Et+RT+St)+0.4\times Ar$

ea(LL)×(EL+RL+SL)+nail involvement score) provides a weighted composite measure reflecting the clinical severity of dermatophytosis across body regions, weighted by their proportional contribution to total body surface area. Adoption of the DSS as the primary objective outcome measure in the Edagajadi Lepa comparative trial represents methodological alignment with contemporary international standards for dermatophytosis clinical trial design.[42]

10. COMPARATIVE ANALYSIS: PRATHAMA VS DVITIYA EDAGAJADI LEPA

The pharmacological superiority of Dvitiya Edagajadi Lepa over Prathama Edagajadi Lepa is theoretically grounded in three key additions:p[8,10,11,12]

Enhanced antifungal spectrum: Sesamin from Tila augments the ergosterol biosynthesis inhibitory activity of anthraquinones from Edagaja through complementary CYP51 targeting, potentially broadening the antifungal spectrum to include *Candida* species and non-dermatophytic moulds that may co-infect Tinea lesions.[12]

Penetration enhancement: The dual penetration-enhancing effects of piperine (P-glycoprotein inhibition, membrane fluidisation) and sesame oil fatty acids (stratum corneum lipid disorder) in Dvitiya Edagajadi Lepa are expected to substantially increase transdermal flux of antifungal constituents to the epidermis and superficial dermis where dermatophytes reside — a capability absent from Prathama Edagajadi Lepa.[11,12]

Anti-inflammatory potency: Piperine's COX-2/5-LOX inhibitory and NF-κB suppressive activities, combined with sesamin's NF-κB pathway modulation, provide more comprehensive attenuation of the inflammatory cascade in Dvitiya Edagajadi Lepa compared to the predominantly antimicrobial (without specific anti-inflammatory) activity profile of Prathama Edagajadi Lepa.[11,12]

Skin barrier restoration: The Twachya and Rasayana properties of Tila seeds, supported by the documented ability of sesame fatty acids to replenish stratum corneum lipids and stimulate fibroblast collagen synthesis, confer superior skin regenerative and relapse-preventive effects on Dvitiya Edagajadi Lepa.[12]

11. PROPOSED CLINICAL TRIAL DESIGN

Based on the pharmacological rationale reviewed above, a single-blind randomised controlled clinical trial with the following parameters is proposed: Group A (n=20) receives Dvitiya

Edagajadi Lepa externally (1/3rd of angushtha thickness, approximately 4–5 mm, applied twice daily with sour gruel) plus Aragvadhadi Kashaya internally (20 mL twice daily before food with equal quantity of water); Group B (n=20) receives Prathama Edagajadi Lepa externally with Aragvadhadi Kashaya internally under identical conditions.[37,38] Primary outcomes include changes in subjective parameters (kandu, raga, pidaka, and udgatam mandala graded on validated 0-4 scales[41]) and objective parameters (number of lesions, lesion area by length x width, KOH microscopic examination, and Dermatophytosis Severity Score).[42] Treatment duration is 45 days with clinical assessments at baseline (day 0), day 15, day 30, and day 45, followed by a 15-day follow-up on day 60. Statistical analysis employs paired t-test and Wilcoxon signed-rank test for within-group comparisons, and Mann-Whitney U-test for between-group comparisons, with a two-tailed significance level of $p < 0.05$. Sample size was calculated based on a minimum clinically important difference in the DSS of 20%, with 80% power and $\alpha = 0.05$.[39]

12. SAFETY PROFILE AND CONTRAINDICATIONS

The constituent drugs of both formulations have well-established safety profiles within Ayurvedic clinical practice. Known contraindications for systemic Aragvadhadi Kashaya include active peptic ulcer disease (due to the bitter/pungent constituents Katuka and Pippali mula potentially stimulating gastric acid secretion), pregnancy (piperine may have uterotonic effects at high doses), and established liver disease.[35] Topically, allergy to any constituent drug necessitates exclusion. The study protocol appropriately excludes subjects with known drug allergies, systemic disease, concomitant dermatological conditions, and those on interfering medications including oral contraceptives and thyroid medications. The 2-week wash-out period before study enrolment ensures freedom from confounding by prior topical or oral antifungal therapy.[39]

13. DISCUSSION

This review presents a multi-dimensional evidence synthesis supporting the mechanistic rationale for the comparative clinical evaluation of Dvitiya versus Prathama Edagajadi Lepa in Dadru Kushta/Tinea corporis. The classical Ayurvedic framework provides not merely empirical drug combinations but a coherent doshic-based pathophysiological model aligning with modern immunological understanding of dermatophytosis — where Kapha vitiation corresponds to the local immune dysregulation facilitating fungal colonisation, and Pitta vitiation corresponds to the erythematous-inflammatory component.

The 'additive ingredients' approach of Dvitiya Edagajadi Lepa — incorporating piperine, sesamin, and expanded salt combination — represents an Ayurvedic application of the modern pharmaceutical principle of multi-target combination therapy. Antifungal combination strategies targeting multiple fungal enzymes simultaneously reduce the probability of resistance emergence, a consideration of particular relevance given the documented emergence of pan-azole-resistant *T. indotineae* in India.[7] The systematic lack of published data specifically on Dvitiya Edagajadi Lepa (zero results on PubMed, DHARA, and AYUSH Research Portal) and Aragvadhadi Kashaya (zero results across all databases) highlights both the novelty and urgent clinical necessity of the proposed research.[39] The robust published evidence base for the constituent drug pharmacology, however, provides strong mechanistic justification for the anticipated clinical outcomes.

14. CONCLUSION

Dadru Kushta, as documented across the major Ayurvedic classical texts from Charaka Samhita through Kashyapa Samhita, represents a well-characterised dermatological entity with a coherent Ayurvedic aetiopathogenesis that maps closely onto the modern understanding of Tinea corporis. The constituent drugs of Dvitiya Edagajadi Lepa and Aragvadhadi Kashaya possess documented phytochemical constituents with multiple antifungal, anti-inflammatory, immunomodulatory, and skin barrier-restorative mechanisms of action. Dvitiya Edagajadi Lepa's compositional advantage over Prathama Edagajadi Lepa lies principally in the addition of Pippali (piperine), Tila (sesamin, fatty acids), and Lavana traya (keratolytic/penetration-enhancing salts), which collectively confer: (a) augmented antifungal activity through additional ergosterol pathway and membrane targets; (b) enhanced transdermal drug delivery through penetration enhancement; (c) superior anti-inflammatory activity through COX/LOX/NF-κB pathway inhibition; and (d) enhanced skin barrier restoration through Twachya and Rasayana mechanisms. The proposed randomised controlled clinical trial, employing validated outcome measures including the Dermatophytosis Severity Score,[42] KOH microscopic examination, and standardised subjective symptom grading,[41] is scientifically well-designed to generate Level IIa clinical evidence for this traditional Ayurvedic therapeutic approach. The results of this trial are anticipated to contribute substantially to evidence-based integration of Ayurvedic dermatophytosis management into mainstream clinical practice, offering safer alternatives to conventional antifungal therapy with its associated risks of hepatotoxicity and emerging drug resistance.

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