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Review

Gut-Derived Immune Activation in Rheumatoid Arthritis: A Conceptual Parallel to *Ama* in *Amavata*

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Abstract

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease in which clinically apparent synovitis is preceded by a prolonged preclinical phase characterized by immune dysregulation and autoantibody formation. Growing evidence implicates gut dysbiosis, impaired intestinal barrier integrity, and gut-derived immune priming as upstream contributors to RA pathogenesis, occurring years before overt joint inflammation. In parallel, Ayurveda describes *Amavata* as a chronic systemic disorder arising from the formation of *Ama*, a pathogenic burden produced by impaired digestive and metabolic function (*Agni*), which accumulates silently, disseminates systemically, and later localizes to the joints. This conceptual review explores a functional correspondence between the Ayurvedic construct of *Ama* in *Amavata* and contemporary models of gut-derived immune activation in RA. Drawing on peer-reviewed biomedical and Ayurvedic literature, the paper examines shared temporal and systemic features of disease development, emphasizing that both frameworks locate disease initiation upstream of overt inflammation. *Ama* is interpreted not as inflammation or tissue injury, but as a preclinical, systemic pathogenic state—functionally analogous to chronic gut dysbiosis, barrier dysfunction, and immune priming described in RA. The proposed mapping is explicitly heuristic and non-reductive. It does not assert one-to-one equivalence between Ayurvedic and biomedical entities, nor does it seek to translate *Ayurveda* into molecular terms. Instead, it highlights a many-to-one contrast in explanatory logic: *Ayurveda* integrates multiple upstream processes into a single unifying construct, whereas biomedicine analytically separates them into discrete mechanisms. By situating both *Amavata* and RA within a shared preclinical, systemic disease logic, this framework reinforces the importance of early, preventive intervention targeting metabolic and gut-immune dysregulation prior to irreversible joint damage. The analysis demonstrates convergent reasoning across distinct medical traditions and supports integrative, systems-oriented perspectives on chronic inflammatory disease initiation.

Keywords: rheumatoid arthritis; preclinical rheumatoid arthritis; gut-joint axis; gut dysbiosis; intestinal permeability; immune priming; autoantibodies; *Amavata*; *Ama*; *Agni*; Ayurveda; integrative medicine; preventive intervention

Introduction

Rheumatoid Arthritis (RA) is an autoimmune disease, which involves chronic synovitis, pannus development, cartilage deformation and bone erosion if left untreated. [1] Although inflammation is central to the pathogenesis of rheumatoid arthritis, disease onset begins years before the appearance of clinical symptoms. [2] In general, the disease affects multiple joints symmetrically, predominantly smaller joints on extremities. [3] By 2020, an estimated 17.6 million people were living with rheumatoid arthritis globally, with a higher prevalence in females. Rheumatoid arthritis imposes a substantial global burden by impairing participation in occupational and societal activities. Despite

a reduction in mortality over recent decades, the global prevalence of rheumatoid arthritis is projected to increase, with an estimated 31.7 million individuals affected worldwide by 2050. [4]

While the exact etiology of the disease is still unknown, recently accumulating evidence indicates that the gut microbiota plays a significant role in the development and progression of RA. [5] Gut dysbiosis, being an altered intestinal microbiota composition, has been associated with impaired intestinal permeability, potentially causing persistent inflammatory responses. Importantly, accumulating evidence suggests that pathogenic immune processes contributing to rheumatoid arthritis may originate in the gut [6] and precede the onset of overt joint inflammation [2] by several years.

Ayurveda, a classical medical system originating in the Indian subcontinent, [7] describes a condition called *Amavata*, frequently correlated in contemporary literature with RA. [8] Classical Ayurvedic literature describes it as a condition arising from the formation of *Ama* – a product of a poorly functioning digestive function, known as *Agni* in *Ayurveda*. [9] Post formation, *Ama* is circulated around the body by *Vata Dosha* and lodged in joints, which are known as *Kaphasthana*. [10] This produces localised swelling, pain and stiffness at affected joints, [11] usually worsening over time. [12]

Despite parallels noted in contemporary Ayurvedic literature [8,10,11] a clear conceptual framework integrating the Ayurvedic concept of *Ama* with modern gut-immune models of RA pathogenesis remains lacking. *Ama* is traditionally described as a systemic pathogenic burden arising from impaired digestive and metabolic function, preceding main symptoms of disease, in this case, the overt inflammatory manifestations. This paper explores whether *Ama* can be interpreted as functionally analogous to gut-derived immune triggers implicated in rheumatoid arthritis, and possibly generate insights, aimed at producing better treatment for RA, as even though multiple therapeutic strategies have been proved to be effective for RA, about 40% of patients are still not able to reach clinical remission. [2] This review draws primarily on contemporary, peer-reviewed Ayurvedic literature to ensure conceptual accessibility to a biomedical readership.

***Amavata*: A Closer Look**

Amavata, described in *Ayurveda*, is a systemic disease, chronic in nature, [10] characterized by stiffness, pain and swelling [13] that culminates in inflammatory multiple joint manifestations. [14]

The word *Amavata* is a combination of two words, “*Ama*” and “*Vata*”. [10]

Ama is a concept, defined as the product of an impaired digestion, resulting as a consequence of weakened digestive capacity, also known as *Agni*. [9] *Agni*, in its physiological state, is the primary entity for metabolic changes at physiological and cellular levels. On the contrary, weakened *Agni* leads to production of *Ama* – a pathogenic, metabolically unprocessed substrate of metabolism. The word “*Ama*” can be translated as “immature” or “incompletely digested”. [15] Classical descriptions characterize *Ama* using qualitative attributes such as heaviness, stickiness, toxicity and unctuousness. In the present analysis, these descriptions are interpreted functionally, framing *Ama* as a pathogenic, metabolically unprocessed substrate arising from impaired digestion and metabolism.

While the degree of *Ama* involvement can vary, it is considered to be a preliminary factor in pathogenesis of most diseases, within the framework of Ayurvedic medicine. [14] Per se, *Ama* itself is *not* a symptom, inflammation or tissue damage, nor does it cause the disease immediately. *Ama* accumulates slowly over a prolonged period of time, which explains the chronic nature of the disease. In the context of *Amavata*'s pathogenesis, *Ama* formation and manifestation is explicitly stated to precede the clinical manifestation of symptoms.

The word *Vata*, in this context, is referring to *Vata Dosha*. In *Ayurveda*, *Doshas* are considered as fundamental pathophysiological entities, essential for the functioning of human body. [15] However, from the standpoint of contemporary medical science, they cannot be equated with any particular system, organ, cell or pathway. Within the *Ayurveda* framework, properly functioning *Vata Dosha* is the primary force in enabling physiological sensory and motor functions for maintenance of health. [16] Disrupted *Vata Dosha* however is the responsible force for the possible movement of *Ama* around

the body [10] and its later involvement with the multiple joints of the individual, producing pain, tenderness, stiffness and swelling, [8] as well as possible feeling of heaviness in the body, loss of appetite, general malaise and fever. [11]

Systemic circulation of *Ama* enabled by *Vata Dosha* provides a functional explanation for the involvement of multiple joints and the presence of generalized symptoms before localized inflammatory manifestations become evident. *Ayurveda's* understanding of *Amavata's* pathogenesis hence implies a pre-clinical system-wide pathogenic state that clearly precedes the clinical manifestation of the disease.

Systemic Nature of RA

Rheumatoid Arthritis is a chronic, systemic autoimmune disorder characterized by persistent inflammatory synovitis, progressive joint destruction, and extra-articular manifestations, resulting in long-term disability worldwide. [17] Clinically, RA most commonly presents as symmetrical involvement of small peripheral joints associated with pain, swelling, tenderness and morning stiffness persisting for six weeks or longer, accompanied by systemic inflammatory activity. [18]

Although environmental factors such as tobacco exposure and various infections have been implicated in disease susceptibility, the precise mechanisms initiating RA remain incompletely understood. [19] Current understanding of pathogenesis of RA, which includes production of autoantibodies, mediation of immune cells, activation of inflammatory pathways, and proliferation of synovium, till date, has not offered us enough support to find a reliable cure for RA. [2] Accumulating evidence indicates that RA development is preceded by a prolonged asymptomatic phase, commonly referred to as 'preclinical RA'. During this period, immune dysregulation is already established in the absence of clinically apparent synovitis, as demonstrated by the presence of rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs), along with broader systemic inflammatory and immunologic abnormalities, years before the onset of overt arthritis. [19] It is noted that ACPAs not only serve as specific biomarkers that reflecting the immune dysfunction of RA, but also play an important role in accelerating the inflammatory response in joints. Furthermore, ACPAs are predictive to bone erosion and cardiovascular diseases as well. [2]

Gut Dysbiosis, Barrier Dysfunction and Immune Priming

The development of rheumatoid arthritis is characterized by a **gap** between the initial break in immune tolerance and the eventual onset of clinical joint inflammation. [20,21] **Preclinical RA** (or pre-RA) is a recognized biomedical concept describing a retrospectively defined period lasting up to 15 years in some individuals, where RA-associated autoantibodies and other disease-related biomarkers are elevated without evidence of inflammatory arthritis. [19,20] Earliest detectable immune abnormalities include the appearance of hallmark antibodies, such as anti-citrullinated protein antibodies (ACPAs) and **Rheumatoid Factor (RF)**, which often increase in titer and expand in epitope variety as the disease approaches. [6,20] **Neutrophils** play a critical role in this early phase, particularly through **NETosis**, where the release of neutrophil extracellular traps (NETs) provides a rich source of citrullinated proteins that strongly stimulate immune system and further accelerate the breakdown of self-tolerance, promoting autoimmunity. [2]

RA's pathogenesis is increasingly linked to a **gut-joint axis**, where **altered gut microbiota** (dysbiosis) is thought to directly contribute to **barrier dysfunction**. [6,22] In this model, microbial or dietary stimuli trigger the secretion of **zonulin**, an enterotoxin that disengages tight junction proteins like ZO-1 and occludin, causing "intestinal leakage". [6,23] This **increased permeability** allows the **translocation of microbial products**, such as DNA, cell wall fragments, and lipopolysaccharides (*microbial parts*), into the systemic circulation and mesenteric lymph nodes. [6,22] The resulting systemic immune activation promotes the differentiation of autoreactive B and T cells within gut-associated lymphoid tissues and facilitates their migration to secondary lymphoid organs and the

synovium, where they contribute to inflammatory processes that cause cartilage and bone damage. [6,22,24,25]

Immune priming can occur within the gut, where the intestinal microbiota is increasingly implicated in the development of abnormal (*aberrant*) systemic immune responses. [20,21] This process involves interactions between resident microbes and host factors that may contribute to a breakdown of mucosal immune tolerance. **Once tolerance is compromised, gut-primed immune cells and microbial products can access the systemic circulation, promoting sustained immune activation at distant sites.** [6,26] Importantly, such widespread immune activation does not require an acute infection; rather, it is thought to arise in the context of chronic gut dysbiosis – a long-standing microbial imbalance that can precede the clinical onset of joint inflammation by many years. [6,20]

Conceptual Mapping: *Ama* and Gut-Derived Immune Activation

This section explores a conceptual correspondence between two explanatory frameworks originating from distinct medical systems: the Ayurvedic concept of *Ama* in the pathogenesis of *Amavata*, and the role of gut dysbiosis-driven immune activation in the development of RA.

Within Ayurvedic pathophysiology, *Ama* is described as a primary pathogenic factor that precedes and contributes to the development of multiple disease states. It is not defined as inflammation, tissue injury, or a discrete pathological lesion, but rather as a preclinical pathological condition arising from impaired digestive and metabolic function. In the absence of overt disease, the presence of *Ama* may manifest only as nonspecific gastrointestinal or systemic symptoms, such as abdominal heaviness, bloating, or altered bowel habits, which are traditionally attributed to dietary irregularities and suboptimal lifestyle factors.

In the context of *Amavata*, *Ama* can be functionally interpreted as a gut-originating pathogenic burden that exists prior to overt inflammatory disease. According to Ayurvedic theory, this burden is systemically distributed by dysregulated *Vata* and subsequently localizes to the joints, where clinical disease becomes apparent. This sequence is conceptually analogous to contemporary models in which gut dysbiosis leads to impairment of the intestinal barrier, increased permeability, translocation of microbial components, and subsequent systemic immune activation that ultimately targets synovial tissues.

It is important to note that this comparison does not imply a one-to-one equivalence between *Ama* and any single biomedical entity. Rather, the mapping is inherently many-to-one: *Ayurveda* integrates multiple biological processes – including metabolic inefficiency, microbial imbalance, barrier dysfunction, and immune priming – into a single unifying construct, whereas biomedical science analytically decomposes these processes into discrete molecular, cellular, and immunological mechanisms. The proposed mapping therefore serves as a functional and heuristic framework rather than a literal translation between systems.

Temporal Logic of Disease Development

In Ayurvedic theory, disease onset is not defined by the appearance of clinical symptoms. Pathogenesis is conceptualized as a time-bound process described as *Shatkriya Kala*, a six-stage model of disease evolution. The early stages involve impairment of digestive and metabolic function (*Agni*), disruption of normal Dosha activity, and gradual accumulation of *Ama*. These changes precede systemic dissemination of pathogenic factors and occur well before tissue localization and overt clinical manifestations.

Although the classical description of *Amavata* does not always enumerate each stage explicitly, its pathogenesis conforms to this temporal framework. Disease development progresses from weakened *Agni* to *Ama* accumulation, followed by dysregulation of *Vata*, which facilitates systemic dissemination of *Ama*. Clinical disease emerges only after this prolonged subclinical phase, when pathogenic factors localize to the joints. In this model, *Ama* accumulates silently and systemically

over time, while dissemination precedes tissue-specific symptom expression, marking clinical presentation as a relatively late event.

A comparable temporal structure is observed in contemporary models of rheumatoid arthritis (RA). Environmental, dietary, and microbial factors may gradually induce gut dysbiosis, which subsequently impairs intestinal barrier integrity. Increased intestinal permeability permits translocation of microbial components into systemic circulation, initiating immune dysregulation and autoantibody formation. These immunological changes precede synovial inflammation and may persist for years before the onset of clinically apparent arthritis. As in *Amavata*, systemic dissemination and immune priming occur prior to localization of pathology within the joints.

Shared Functional Characteristics

Both *Ama*-related pathology and gut-derived immune activation represent upstream processes in disease development, occurring prior to overt inflammation. In early stages, both are systemic rather than organ-specific, may persist for prolonged periods without clear clinical symptoms, and are non-infectious in nature. Neither constitutes inflammation per se, yet both predispose specific tissues to later pathological involvement. These shared functional properties help explain the chronic, relapsing course of disease and support a model in which systemic dissemination precedes localized clinical manifestations.

Rationale and Conceptual Utility of the Analogy

This conceptual analogy reframes rheumatoid arthritis (RA) as a disease whose earliest clinically relevant phase occurs upstream of overt inflammation, aligning with contemporary models of preclinical RA as well as classical Ayurvedic descriptions of *Amavata* pathogenesis. By positioning both conditions within a preclinical, systemic disease framework, the model emphasizes pathogenic processes that precede synovial inflammation and irreversible tissue damage.

Interpreting the function of *Ama* as conceptually analogous to gut-derived immune triggers provides a coherent explanatory framework for understanding *Amavata* and RA as disorders rooted in early metabolic-immune dysregulation. Within this framework, early intervention targets not merely symptom modulation during established disease, but the prevention of pathological progression itself. This perspective helps contextualize *Ayurveda's* sustained emphasis on digestive function, dietary regulation, and metabolic balance as preventive strategies rather than solely symptomatic treatments.

Importantly, this analogy is not proposed as a retroactive validation of modern immunological findings through Ayurvedic concepts, nor as an attempt to establish conceptual equivalence between distinct medical systems. Instead, it highlights convergent patterns in disease understanding that emerge from fundamentally different epistemological traditions. Contemporary biomedical literature increasingly supports the role of gut-mediated immune priming and subclinical systemic dysregulation in RA pathogenesis, placing these observations within a conceptual space that is functionally compatible with classical Ayurvedic reasoning.

The intent of this comparative model is therefore integrative rather than justificatory: to demonstrate how distinct knowledge systems, despite divergent terminologies and theoretical foundations, may offer complementary perspectives on disease initiation and prevention. Such an approach prioritizes explanatory coherence and clinical utility over ideological alignment, consistent with the primary objective of medicine—to reduce suffering through effective understanding and intervention, irrespective of the originating knowledge framework.

Limitations of the Conceptual Model

This framework does not posit that rheumatoid arthritis arises from a uniform, gut-mediated mechanism across all patients, nor that the Ayurvedic concept of *Ama* can be reduced exclusively to autoimmune pathology. Accordingly, it does not advance a single causal model or claim a

comprehensive explanatory theory of disease pathogenesis. Instead, it identifies a plausible domain of conceptual convergence within a clinically and biologically heterogeneous, multifactorial disease, where distinct explanatory systems may intersect without implying equivalence or exhaustiveness.

Conclusions

This review examined a functional correspondence between the Ayurvedic concept of *Ama* in *Amavata* and contemporary models of gut-derived immune activation in rheumatoid arthritis (RA). By placing both frameworks within a preclinical, systemic model of disease development, it highlights a shared temporal logic in which pathogenic processes precede overt inflammation and irreversible joint damage. In both systems, disease initiation is not defined by synovitis itself, but by upstream disturbances that silently accumulate and disseminate before localizing to the joints.

Within *Ayurveda*, *Ama* represents a systemic pathogenic burden arising from impaired digestion and metabolism, accumulating gradually and remaining clinically subtle until mobilized by dysregulated *Vata*. In modern biomedical models, gut dysbiosis, barrier dysfunction, and immune priming similarly precede clinical RA by years, manifesting initially as subclinical immune abnormalities such as autoantibody formation. Although these concepts emerge from distinct epistemological traditions and are articulated in different terminologies, they converge functionally as upstream, non-infectious, systemic drivers of later tissue-specific inflammation.

The proposed mapping does not claim equivalence between *Ama* and any single immunological or microbial entity, nor does it seek to reduce *Ayurveda* to molecular mechanisms. Rather, it demonstrates how *Ayurveda* integrates multiple upstream processes – metabolic inefficiency, microbial imbalance, systemic dissemination, and immune susceptibility into a single unifying construct, whereas biomedical science analytically separates these phenomena. This many-to-one versus one-to-many contrast underscores the complementary strengths of both systems.

Conceptually, this framework reinforces the importance of early, preventive intervention in RA, targeting metabolic and gut-immune dysregulation before irreversible joint pathology develops. It also provides a coherent rationale for *Ayurveda*'s long-standing emphasis on digestive function, diet, and systemic balance as central therapeutic priorities rather than adjunctive measures. By aligning classical Ayurvedic reasoning with contemporary evidence on preclinical RA and the gut–joint axis, this model offers an integrative perspective that may support more comprehensive approaches to prevention and early disease modulation.

Ultimately, this work does not aim to validate one system through the other, but to demonstrate that independent medical traditions can arrive at structurally similar understandings of disease initiation through different explanatory pathways. Recognizing such convergences can enrich clinical reasoning, encourage earlier intervention strategies, and support a more nuanced, systems-oriented view of chronic inflammatory diseases such as rheumatoid arthritis.

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Conflicts of Interest: The author declares no conflicts of interest.

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