Review

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

Alexander Dmitriev * , Rahul Gandhi , Girish Tillu

Posted Date: 15 February 2026

doi: 10.20944/preprints202602.0793.v2

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

Review

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

Alexander Dmitriev [1,*], Rahul Gandhi [1] and Girish Tillu [2]

[1] Department of Panchakarma, Institute of Teaching and Research in Ayurveda, Jamnagar, Gujarat, India

[2] AYUSH Centre of Excellence, Department of Health Sciences, Savitribai Phule Pune University, Pune, Maharashtra, India

* Correspondence: alextoysov@gmail.com

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

 doi:10.20944/preprints202602.0793.v2

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.

Methods

Study Design

This is a narrative conceptual review aimed at exploring possible parallels between gut-derived immune activation in rheumatoid arthritis and the concept and function of *Ama* in *Amavata*. It seeks to identify functional correspondences and areas of conceptual convergence rather than to synthesize quantitative evidence or establish causal inferences. This work is not designed as a systematic review and does not follow formal systematic review protocols. It is likewise not a meta-analysis and does not perform statistical aggregation of study outcomes. The objective is interpretative and theoretical, focused on constructing an integrative conceptual model rather than generating pooled empirical estimates.

Literature Search Strategy

The literature for this paper was collected using PubMed. The search period extended from database inception to January 2026. Representative keywords included: "*Ama*," "*Amavata*," "*Ayurveda*," "*Dosha*," "rheumatoid arthritis," "preclinical rheumatoid arthritis," "gut-joint axis," and "gut microbiota." Articles were manually reviewed to ensure they directly supported the conceptual focus of the paper. The reference lists of relevant papers were also checked manually to find additional useful studies. Given the nature of this work, formal systematic review protocols, predefined inclusion/exclusion criteria, and quantitative synthesis methods were not applied.

 doi:10.20944/preprints202602.0793.v2

Selection Criteria

Studies were considered eligible for conceptual inclusion if they were peer-reviewed biomedical publications addressing rheumatoid arthritis, preclinical rheumatoid arthritis, gut dysbiosis, immune priming, intestinal permeability, or related mechanisms of early immune activation. Contemporary peer-reviewed Ayurvedic research articles discussing *Dosha*, *Amavata*, *Ama* in pathophysiological context were also included. Preference was given to studies explaining how disease begins, not studies mainly testing therapies or symptom control. Methodological hierarchy of therapeutic evidence was not the primary determinant of inclusion, as the objective was mechanistic and conceptual rather than interventional.

Analytical Framework

This review employed a structured comparative framework designed to analyze explanatory correspondences between Ayurvedic and biomedical models without assuming ontological equivalence. The mapping was conducted at the level of functional role in pathogenesis rather than at the level of material or molecular identity. Constructs were compared based on their position within disease development, their systemic versus localized nature, and their upstream or downstream relationship to overt inflammatory pathology.

The first axis of comparison was temporal structure. Both *Amavata* and rheumatoid arthritis were analyzed along a disease-evolution process beginning from early subclinical disturbance to overt joint inflammation. Correspondence was identified where both systems describe a prolonged preclinical phase characterized by systemic pathogenic activity preceding synovitis. *Ama* accumulation within impaired *Agni* function was therefore compared with immune dysregulation, autoantibody formation, and gut-derived immune priming described in preclinical rheumatoid arthritis.

The second axis involved shared functional characteristics. Constructs were evaluated according to whether they: 1) operate systemically rather than as organ-confined lesions, 2) precede overt tissue damage, 3) persist chronically and cumulatively, and 4) predispose tissues to later inflammation without constituting inflammation themselves. Functional similarity under these criteria served as the basis for heuristic alignment, independent of biochemical equivalence.

The third axis examined explanatory structure. Ayurvedic pathophysiology integrates multiple upstream processes – metabolic impairment, accumulation, dissemination, and susceptibility – into a unified construct (*Ama*), reflecting a many-to-one explanatory logic. In contrast, contemporary biomedical models decompose disease initiation into discrete mechanisms such as dysbiosis, barrier dysfunction, neutrophil extracellular trap formation, and adaptive immune priming, reflecting a one-to-many analytical logic. The comparison therefore evaluates structural differences in explanatory organization rather than attempting direct conceptual translation.

This framework is explicitly heuristic and non-reductive. It does not assert that *Ama* corresponds to a specific microbial species, immune mediator, or molecular pathway. Instead, it identifies functional convergence within the domain of early systemic disease initiation while preserving the epistemological integrity of both medical systems.

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

 doi:10.20944/preprints202602.0793.v2

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

 doi:10.20944/preprints202602.0793.v2

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 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.

 doi:10.20944/preprints202602.0793.v2

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.

Discussion

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

 doi:10.20944/preprints202602.0793.v2

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.

Competing Models of RA Initiation

In addition to gut-origin hypotheses, lung-origin hypothesis proposes that the respiratory tract is a primary site where the initial breach of immune tolerance occurs, leading to the development of seropositive RA. Evidence shows that RA-related autoantibodies, such as anti-citrullinated protein antibodies (ACPA), are produced locally within the lung mucosa and sputum of at-risk individuals long before joint inflammation becomes clinically apparent. (27,28)

The periodontal hypothesis suggests that chronic inflammation in the mouth, specifically periodontitis, plays a causal role in RA pathogenesis. A central element of this model is the bacterium Porphyromonas gingivalis, which is unique for its ability to produce an enzyme (PPAD) that citrullinates proteins. This oral dysbiosis can trigger a local ACPA response in the periodontium that may eventually spread systemically through epitope spreading, illustrating another mucosal pathway independent of the gastrointestinal tract. (28,29)

The genetic susceptibility model proposes that immune triggers at mucosal surfaces interact with a person's genetic background to promote progression from local inflammation to systemic rheumatoid arthritis. The strongest genetic factor is the *HLA-DRB1* "shared epitope" (SE), which increases the risk of ACPA-positive RA, especially in combination with environmental exposures such as smoking. Although immune activation may begin in the lung or oral mucosa, the SE likely promotes systemic autoimmunity by efficiently presenting citrullinated antigens to immune cells. (28,30)

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.

Current Research Gaps

A primary challenge in current research is determining whether gut dysbiosis is a cause or a consequence of rheumatoid arthritis, as establishing a definitive causal relationship remains difficult. (23,25) While the "gut-joint axis" is widely recognized, the exact translocation mechanisms by which bacterial components or live microbes move from the intestinal lumen to joint tissues are not yet fully understood. (6,31) Furthermore, there is significant debate regarding the primary anatomic site of initial disease triggering, with various mucosal surfaces like the gut, lungs, and mouth all being potential candidates. (6,19,20) Methodologically, many studies are limited by an over-reliance on fecal samples, which may not accurately reflect the actual microbial environment of the intestinal mucosa where immune priming occurs. (23,26) Additionally, many microbial shifts observed in patients appear to be non-specific alterations shared across multiple rheumatic conditions rather than unique, disease-specific biological differences. (25)

 doi:10.20944/preprints202602.0793.v2

Future Directions

Future research directions are shifting toward precision and personalized medicine that utilizes individual microbiome profiles and synovial biomarkers to tailor therapies for each patient. (2) Significant efforts are being directed toward restoring the intestinal barrier through the use of zonulin antagonists like larazotide acetate or by leveraging short-chain fatty acids to treat "leaky gut". (1,24) Other promising avenues include the development of epigenetic and metabolic regulators to reprogram pathogenic immune cells and the exploration of advanced cell therapies, such as engineered CAR-T cells and mesenchymal stem cells. Clinical management is also moving toward stage-specific interventions, recognizing that microbial and metabolic patterns vary across the four distinct clinical stages of RA. Ultimately, a major goal is preclinical prevention, identifying and treating high-risk individuals before the transition from asymptomatic autoimmunity to inflammatory arthritis begins. (2)

Conclusion

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.

Data Availability: Not applicable. No datasets were generated or analyzed during this study.

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

 doi:10.20944/preprints202602.0793.v2

References

1. Xu X, Wang M, Wang Z, Chen Q, Chen X, Xu Y, et al. The bridge of the gut–joint axis: Gut microbial metabolites in rheumatoid arthritis. Front Immunol [Internet]. 2022 Oct 6 [cited 2026 Jan 28];13. Available from: https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2022.1007610/full
2. Gao Y, Zhang Y, Liu X. Rheumatoid arthritis: pathogenesis and therapeutic advances. MedComm. 2024;5(3):e509.
3. Chauhan K, Jandu JS, Brent LH, Al-Dhahir MA. Rheumatoid Arthritis. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2026 Jan 28]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK441999/
4. GBD 2021 Rheumatoid Arthritis Collaborators. Global, regional, and national burden of rheumatoid arthritis, 1990-2020, and projections to 2050: a systematic analysis of the Global Burden of Disease Study 2021. Lancet Rheumatol. 2023 Oct;5(10):e594–610.
5. Chen S, Hoang MH, Hu D, He Q, Gao Y. Gut microbiota in early and established stages of rheumatoid arthritis: from pathogenesis to promising prevention and treatment. Ann Med. 58(1):2613484.
6. Romero-Figueroa M del S, Ramírez-Durán N, Montiel-Jarquín AJ, Horta-Baas G. Gut-joint axis: Gut dysbiosis can contribute to the onset of rheumatoid arthritis via multiple pathways. Front Cell Infect Microbiol. 2023 Jan 27;13:1092118.
7. Pan SY, Litscher G, Gao SH, Zhou SF, Yu ZL, Chen HQ, et al. Historical Perspective of Traditional Indigenous Medical Practices: The Current Renaissance and Conservation of Herbal Resources. Evid Based Complement Alternat Med. 2014;2014(1):525340.
8. Gupta SK, Thakar AB, Dudhamal TS, Nema A. Management of Amavata (rheumatoid arthritis) with diet and Virechanakarma. AYU Int Q J Res Ayurveda. 2015 Dec;36(4):413.
9. Pandey P, Rastogi S, Lawrence A, Agrawal GG. Development and validation of an *ama* instrument for assessing the disease activity on the basis of constitutional features in *Amavata* (Rheumatoid Arthritis). J Ayurveda Integr Med. 2023 Mar 1;14(2):100689.
10. Aswathy YS, Anandaraman PV. Therapeutic influence of some dietary articles on gut microbiota in the pathogenesis of rheumatoid arthritis (Amavata) – A review. Ayu. 2019;40(3):147–51.
11. Maragalawaththa MGSK, Goyal M. Efficacy of Seetarama Vati (A Sri Lankan traditional drug) and Vatari Guggulu in the management of Amavata (rheumatoid arthritis)-an open labeled randomized comparative clinical trial. Ayu. 2019;40(2):97–103.
12. Makhija D, Mata S, Sharma A, Kachare K, Manathottathil A, Jain S, et al. Effectiveness of Composite Ayurveda Regimen in a Black Box Design for the Management of Rheumatoid Arthritis: Protocol of a Single Arm, Community-Based Study. JMIR Res Protoc. 2025 Feb 18;14(1):e57918.
13. Singh JP, Antiwal M, Vaibhav A, Tripathi JS, Tiwari SK. Clinical efficacy of Rasona Pinda in the management of Amavata (rheumatoid arthritis). Ayu. 2010;31(3):280–6.
14. Wagh S, Raut A. Aam assessment instrument for disease activity in *Aamavata*: Scope and challenges. J Ayurveda Integr Med. 2023 Nov 1;14(6):100816.
15. Sumantran VN, Tillu G. Cancer, Inflammation, and Insights from Ayurveda. Evid Based Complement Alternat Med. 2012;2012(1):306346.
16. Sumantran VN, Nair PP. Can the vagus nerve serve as biomarker for *vata dosha* activity? J Ayurveda Integr Med. 2019 Apr 1;10(2):146–51.
17. Mao CL, Yu CH, Jiang SL, Ying ZH, Zhu XY. Neutrophil extracellular traps in rheumatoid arthritis: pathogenic mechanisms and therapeutic potential. Front Immunol. 16:1717671.
18. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis. 2010 Sep 1;69(9):1580–8.
19. Deane KD. Preclinical Rheumatoid Arthritis (Autoantibodies): An Updated Review. Curr Rheumatol Rep. 2014 May;16(5):419.
20. Mankia K, Emery P. Review: Preclinical Rheumatoid Arthritis: Progress Toward Prevention. Arthritis Rheumatol. 2016;68(4):779–88.

 doi:10.20944/preprints202602.0793.v2

21. Scher JU, Sczesnak A, Longman RS, Segata N, Ubeda C, Bielski C, et al. Expansion of intestinal Prevotella copri correlates with enhanced susceptibility to arthritis. Mathis D, editor. eLife. 2013 Nov 5;2:e01202.
22. Zhao T, Wei Y, Zhu Y, Xie Z, Hai Q, Li Z, et al. Gut microbiota and rheumatoid arthritis: From pathogenesis to novel therapeutic opportunities. Front Immunol. 2022 Sep 8;13:1007165.
23. Audo R, Sanchez P, Rivière B, Mielle J, Tan J, Lukas C, et al. Rheumatoid arthritis is associated with increased gut permeability and bacterial translocation that are reversed by inflammation control. Rheumatology. 2023 Mar 1;62(3):1264–71.
24. Tajik N, Frech M, Schulz O, Schälter F, Lucas S, Azizov V, et al. Targeting zonulin and intestinal epithelial barrier function to prevent onset of arthritis. Nat Commun. 2020 Apr 24;11(1):1995.
25. Wang Y, Wei J, Zhang W, Doherty M, Zhang Y, Xie H, et al. Gut dysbiosis in rheumatic diseases: A systematic review and meta-analysis of 92 observational studies. EBioMedicine. 2022 Jun;80:104055.
26. Chiang HI, Li JR, Liu CC, Liu PY, Chen HH, Chen YM, et al. An Association of Gut Microbiota with Different Phenotypes in Chinese Patients with Rheumatoid Arthritis. J Clin Med. 2019 Oct 24;8(11):1770.
27. Joshua V, Loberg Haarhaus M, Hensvold A, Wähämaa H, Gerstner C, Hansson M, et al. Rheumatoid Arthritis–Specific Autoimmunity in the Lung Before and at the Onset of Disease. Arthritis Rheumatol. 2023;75(11):1910–22.
28. Holers VM, Demoruelle MK, Kuhn KA, Buckner JH, Robinson WH, Okamoto Y, et al. Rheumatoid Arthritis and the Mucosal Origins Hypothesis: External Protection Becomes Internal Destruction. Nat Rev Rheumatol. 2018 Sep;14(9):542–57.
29. Li Y, Guo R, Oduro PK, Sun T, Chen H, Yi Y, et al. The Relationship Between Porphyromonas Gingivalis and Rheumatoid Arthritis: A Meta-Analysis. Front Cell Infect Microbiol [Internet]. 2022 Jul 18 [cited 2026 Feb 11];12. Available from: https://www.frontiersin.org/journals/cellular-and-infection-microbiology/articles/10.3389/fcimb.2022.956417/full
30. Holoshitz J. The Rheumatoid Arthritis HLA-DRB1 Shared Epitope. Curr Opin Rheumatol. 2010 May;22(3):293–8.
31. Cheng M, Zhao Y, Cui Y, Zhong C, Zha Y, Li S, et al. Stage-specific roles of microbial dysbiosis and metabolic disorders in rheumatoid arthritis. Ann Rheum Dis. 2022 Dec;81(12):1669–77.