ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26jan387

The Gut Microbiome and Rheumatoid Arthritis: A Hidden Driver of Autoimmunity and an Emerging Therapeutic Target

Dibyendu Raj[1*]

[1.] Department of Biochemistry, Vivekananda College, Thakurpukur, Kolkata-700063, WB, India.

Corresponding Author: Dibyendu Raj*

Publication Date: 2026/01/20

Abstract: Rheumatoid arthritis (RA) is a chronic, systemic, immune-mediated inflammatory disease characterized by persistent synovitis, progressive joint destruction, functional disability, and a wide spectrum of extra-articular manifestations. Despite substantial advances in disease-modifying therapies, RA continues to impose a significant global health burden, with rising prevalence and substantial socioeconomic costs. In recent years, growing attention has been directed toward the gut–immune axis, revealing the gut microbiota as a central regulator of immune homeostasis and a potential driver of autoimmune diseases, including RA. Accumulating evidence from animal models, human cohort studies, and translational research indicates that alterations in gut microbial composition and function—collectively referred to as dysbiosis—may precede clinical disease onset, influence immune tolerance, and modulate disease severity and therapeutic response. This comprehensive review integrates current knowledge on the epidemiology, etiology, immunopathogenesis, and systemic manifestations of RA, with a particular emphasis on the mechanistic and translational role of the gut microbiome. We discuss microbial–host interactions, immune pathways, emerging microbiome-derived biomarkers, and evolving microbiota-targeted therapeutic strategies, highlighting their potential to reshape the future of personalized RA management.

Keywords: *Rheumatoid Arthritis, Gut Microbiome, Pro-Inflammatory Immune Responses, Autoimmunity, Gut-Joint Connection, Microbiome Science.*

How to Cite: Dibyendu Raj (2026) The Gut Microbiome and Rheumatoid Arthritis: A Hidden Driver of Autoimmunity and an Emerging Therapeutic Target. *International Journal of Innovative Science and Research Technology*, 11(1), 1103-1110. https://doi.org/10.38124/ijisrt/26jan387

I. INTRODUCTION

Rheumatoid arthritis (RA) is one of the most prevalent and debilitating autoimmune rheumatic diseases, affecting millions of individuals worldwide and representing a major cause of chronic pain, disability, and reduced quality of life. According to global estimates from 2020, approximately 17.6 million people were living with RA, with projections suggesting that this number may increase to over 31 million by 2050 due to population aging, urbanization, and changing environmental exposures [1]. In India, epidemiological data indicate an annual incidence of 20–40 cases per 100,000 individuals, underscoring the growing public health relevance of RA in both developed and developing nations [2].

Clinically, RA is characterized by symmetric polyarthritis predominantly involving the small joints of the hands and feet, accompanied by hallmark features such as joint swelling, tenderness, and prolonged morning stiffness. As the disease progresses, persistent synovial inflammation leads to cartilage degradation, bone erosion, joint deformity, and irreversible functional impairment. In addition to musculoskeletal involvement, RA is increasingly recognized as a systemic disease with extra-articular manifestations affecting the lungs, cardiovascular system, skin, eyes, nervous system, and hematopoietic organs. These systemic features significantly contribute to increased morbidity, premature mortality, and healthcare utilization [3].

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26jan387

RA can affect individuals across the lifespan, including children and adolescents (juvenile rheumatoid arthritis), although it most commonly presents between the ages of 35 and 60 years. The disease exhibits a strong female predominance, with women affected approximately two to three times more frequently than men, suggesting a role for hormonal and sex-specific immunological factors. Despite extensive research, the precise etiology of RA remains incompletely understood, and no definitive cure currently exists. Contemporary therapeutic strategies primarily focus on symptom control, suppression of inflammation, and prevention of structural damage, with variable efficacy among individuals [4].

Over the past two decades, a paradigm shift has occurred in our understanding of autoimmune diseases, driven by insights into the complex interplay between host genetics, environmental exposures, immune regulation, and the microbiome. The human gastrointestinal tract harbors trillions of microorganisms—collectively referred to as the gut microbiota—that form a dynamic and metabolically active ecosystem. This microbial community plays a critical role in shaping immune development, maintaining mucosal tolerance, and regulating systemic inflammatory responses. Disruption of this delicate balance, termed dysbiosis, has been increasingly linked to the initiation and progression of autoimmune and inflammatory diseases, including inflammatory bowel disease, multiple sclerosis, type 1 diabetes, and RA [3].

Emerging evidence suggests that alterations in gut microbiota composition and function may precede the clinical onset of RA, acting as environmental triggers that influence immune tolerance, intestinal barrier integrity, and systemic inflammation. Specific microbial taxa and microbial-derived metabolites have been implicated in modulating T-cell differentiation, promoting pro-inflammatory pathways, and contributing to the immune dysregulation characteristic of RA. These findings have fueled interest in the gut microbiome not only as a mechanistic contributor to RA pathogenesis but also as a potential source of diagnostic biomarkers and therapeutic targets.

This review aims to provide an in-depth and integrative analysis of the current literature examining the role of gut microbiota in RA. We explore the epidemiology, etiology, immunopathogenesis, and systemic manifestations of RA, with a particular focus on microbial–host interactions and their translational implications. By synthesizing evidence from basic science, clinical research, and emerging therapeutic approaches, this review seeks to illuminate new avenues for personalized and microbiome-informed management of RA [3].

II. OBJECTIVES OF THE REVIEW

Given the complexity and heterogeneity of RA, a comprehensive and multidisciplinary approach is essential for advancing understanding and improving patient outcomes. The primary objectives of this review are as follows:

- To elucidate the multifactorial etiology and immunopathological mechanisms underlying RA, with particular emphasis on the emerging role of the gut microbiota and its interaction with host genetics and immune pathways.
- To critically examine the contribution of environmental, microbial, and lifestyle factors to RA susceptibility, disease onset, and progression.
- To identify and synthesize evidence on extra-articular manifestations and co-morbidities associated with RA, highlighting their impact on prognosis, quality of life, and mortality.
- To evaluate current and emerging diagnostic biomarkers, including microbiome-based signatures that may facilitate early detection and disease stratification.
- To review existing and novel therapeutic strategies for RA, with a focus on microbiota-modulating interventions and their potential integration into personalized treatment paradigms.
- To underscore the importance of inter professional and multidisciplinary care in the holistic management of RA, encompassing rheumatology, immunology, microbiology, cardiology, pulmonology, and patient-centered care.

By addressing these objectives, this review aims to deepen current understanding of RA pathogenesis and management while identifying gaps in knowledge and opportunities for future research.

III. GLOBAL BURDEN AND EPIDEMIOLOGY OF RHEUMATOID ARTHRITIS

Recent analyses from the Global Burden of Disease Study underscore the growing public health impact of RA [5]. Between 1990 and 2021, the global prevalence and years lived with disability (YLDs) attributable to RA increased substantially, driven by population growth, aging, and improved survival [6]. Black et al. and Ma et al. demonstrated significant regional variation, with the highest age-standardized prevalence rates observed in North America and Western Europe, while South Asia and sub-Saharan Africa showed rapidly rising trends.

In India, RA incidence is estimated at 20–40 cases per 100,000 individuals annually, translating into a considerable socioeconomic burden due to disability during peak working years. Women consistently exhibit higher prevalence rates than men, a disparity attributed to hormonal, genetic, and immunological factors [7]. Importantly, seropositive RA—defined by the presence of rheumatoid factor (RF) and/or anti-

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26jan387

citrullinated protein antibodies (ACPAs)—is associated with more severe disease and higher heritability [8].

The increasing global burden of RA highlights the urgent need for improved strategies for early diagnosis, prevention, and personalized treatment. Understanding environmental contributors such as the gut microbiota may be pivotal in addressing these challenges [9].

➢ *Etiology of Rheumatoid Arthritis*

The etiology of RA is multifactorial and involves a complex interplay between genetic predisposition, environmental exposures, immune dysregulation, and microbial influences. No single factor is sufficient to cause RA; rather, the disease emerges from the convergence of multiple risk determinants that collectively disrupt immune tolerance and promote chronic inflammation.

➢ *Genetic Factors*

Genetic susceptibility plays a pivotal role in RA development, with heritability estimates ranging from 40% to 65% for seropositive disease [10]. The strongest genetic associations have been identified within the major histocompatibility complex (MHC), particularly HLA-DRB1 alleles. Specific alleles such as HLA-DRB1*04*, *HLA-DRB1*01, and HLA-DRB1*10 share a conserved amino acid motif known as the "shared epitope," which is thought to influence antigen presentation and promote the activation of autoreactive T cells [11].

Beyond HLA genes, numerous non-HLA loci have been implicated in RA susceptibility through genome-wide association studies (GWAS). These include genes involved in immune regulation and signaling pathways, such as PTPN22, CTLA-4, STAT4, IL2RA, TRAF1, CCR6, and IRF5. Variants in these genes can alter T-cell activation, cytokine production, and immune tolerance, thereby increasing the risk of autoimmunity [12].

Epigenetic mechanisms also contribute to RA pathogenesis by modulating gene expression without altering the underlying DNA sequence [13]. Aberrant DNA methylation patterns, histone modifications, and dysregulated non-coding RNAs have been observed in synovial fibroblasts, immune cells, and peripheral blood mononuclear cells of RA patients. These epigenetic changes may interact with genetic and environmental factors to perpetuate chronic inflammation and joint destruction.

➢ *Genetic Susceptibility and Host Factors*

Genetic factors contribute substantially to RA risk, with heritability estimates ranging from 40% to 65% for seropositive disease. The strongest genetic association resides within the major histocompatibility complex (MHC) class II region, particularly HLA-DRB1 alleles encoding the so-called "shared epitope." These alleles influence antigen presentation and promote autoreactive T-cell responses against citrullinated peptides [14].

Beyond HLA genes, numerous non-HLA loci have been implicated in RA susceptibility, including PTPN22, CTLA4, STAT4, TRAF1, IL2RA, CCR6, and IRF5. These genes are involved in T-cell activation, immune checkpoint regulation, cytokine signaling, and innate immune responses. Recent reviews by Kurkó et al., Karami et al., and Terao et al. emphasize that genetic variants not only shape immune responses but may also influence gut microbiota composition, thereby linking host genetics to microbial dysbiosis [15].

Epigenetic mechanisms, such as DNA methylation, histone modifications, and non-coding RNAs, further modulate gene expression in RA. Environmental exposures—including smoking, infections, and diet—can induce epigenetic changes that interact with genetic susceptibility to promote autoimmunity.

➢ *Environmental Triggers and Lifestyle Factors*

Environmental exposures play a crucial role in triggering RA, particularly in genetically susceptible individuals. Cigarette smoking is the most well-established environmental risk factor and is strongly associated with anti-citrullinated protein antibodies (ACPAs)-positive RA [16]. Smoking induces oxidative stress, promotes protein citrullination, and enhances antigen presentation, thereby amplifying autoimmune responses. The interaction between smoking and the HLA-DRB1 shared epitope exemplifies a classic gene–environment interaction in RA [17].

Occupational exposures to silica, asbestos, and textile dust have also been linked to increased RA risk, particularly in seropositive patients. Periodontal disease, especially infection with *Porphyromonas gingivalis*, has garnered significant attention due to its unique ability to express peptidyl arginine deiminase enzymes capable of citrullinating host proteins. Dietary factors, including high-calorie, low-fiber Western diets, may promote inflammation and dysbiosis, whereas omega-3 fatty acids appear to exert protective effects. Obesity, hormonal changes, air pollution, and psychosocial stress further contribute to RA susceptibility and disease severity [18].

Dietary patterns influence both systemic inflammation and gut microbiota composition. Western diets rich in saturated fats and low in fiber are associated with increased inflammatory markers, whereas diets enriched in omega-3 polyunsaturated fatty acids, fruits, vegetables, and whole grains may confer protective effects. Obesity, another modifiable risk factor, is associated with chronic low-grade inflammation and altered gut microbiota profiles, further implicating metabolic–microbial interactions in RA [19].

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26jan387

➢ *Immunological Factors*

RA is characterized by a breakdown of immune tolerance and the emergence of autoreactive immune responses. Central to this process is the generation of autoantibodies, particularly rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs). RF is typically an IgM antibody directed against the Fc portion of IgG, forming immune complexes that deposit in synovial tissues and activate complement pathways. ACPAs target citrullinated proteins generated through post-translational modification of arginine residues by peptidyl arginine deiminase enzymes [20].

The formation of immune complexes and activation of innate immune pathways lead to sustained production of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1, IL-6, and IL-17. These cytokines drive synovial hyperplasia, recruitment of inflammatory cells, activation of osteoclasts, and degradation of cartilage and bone. The adaptive immune system, particularly CD4+ T-helper cells and B cells, plays a central role in perpetuating chronic inflammation and tissue damage. These cytokines drive synovial inflammation, fibroblast-like synoviocyte (FLS) activation, and osteoclast-mediated bone resorption [21]. B cells differentiate into plasma cells producing RF and ACPAs, which form immune complexes that activate complement pathways and amplify inflammation. The result is pannus formation, cartilage destruction, and irreversible joint damage. Emerging evidence suggests that immune dysregulation in RA may originate, at least in part, in mucosal sites such as the gut, lung, and oral cavity. Among these, the gut microbiota has emerged as a central player in shaping systemic immune responses [22].

IV. PATHOGENIC PARTNERSHIPS: THE ROLE OF GUT MICROBIOTA IN RHEUMATOID ARTHRITIS

The human gut microbiota represents one of the most complex microbial ecosystems on the planet, comprising bacteria, archaea, viruses, and fungi that collectively influence host physiology and immunity. Approximately 70–80% of the immune system resides within the gastrointestinal tract, highlighting the central role of gut-associated lymphoid tissue in immune surveillance and tolerance. Under physiological conditions, a symbiotic relationship exists between the host and its microbiota, characterized by mutual benefit and immune homeostasis [23].

➢ *Dysbiosis and Immune Dysregulation*

Dysbiosis, defined as an imbalance in microbial composition and function, has been increasingly implicated in RA pathogenesis. Studies in both animal models and human cohorts have demonstrated reduced microbial diversity and altered relative abundance of specific bacterial taxa in RA patients. Dysbiosis can disrupt intestinal barrier integrity by loosening epithelial tight junctions, often mediated by increased zonulin release [24]. This increased permeability allows translocation of microbial components and metabolites into the systemic circulation, where they can activate innate immune cells such as dendritic cells and macrophages [25].

Bacterial components, including peptidoglycans and lipopolysaccharides, have been detected in the synovial tissues of RA patients, suggesting a direct link between gut-derived microbial products and joint inflammation. These microbial signals stimulate pattern recognition receptors, leading to activation of inflammatory pathways and cytokine production [25].

➢ *Microbiota-Mediated T-Cell Differentiation*

Specific gut microbes exert profound effects on T-cell differentiation and immune balance. Segmented filamentous bacteria promote the accumulation of Th17 cells in the intestinal lamina propria, whereas *Bacteroides fragilis* has been shown to enhance regulatory T-cell (Treg) responses through polysaccharide A–mediated mechanisms. An imbalance between pro-inflammatory Th17 cells and immunosuppressive Tregs is a hallmark of RA and is strongly influenced by microbial composition and microbial-derived metabolites such as short-chain fatty acids [26].

Aberrant activation of adaptive immune responses in the gut mucosa can lead to systemic immune dysregulation. Microbial antigens presented by antigen-presenting cells activate CD4+ T cells, driving differentiation into Th1, Th17, and Th2 subsets. These cells migrate to synovial tissues, where they secrete cytokines that perpetuate inflammation and tissue destruction [27].

➢ *Evidence from Human and Animal Studies*

Multiple studies have demonstrated altered gut microbiota composition in RA. Reduced abundance of beneficial commensals such as *Faecalibacterium prausnitzii*, *Bifidobacterium*, and *Eubacterium rectale* has been consistently reported [28]. These bacteria are known to exert anti-inflammatory effects, maintain intestinal barrier function, and promote immune tolerance. Conversely, increased abundance of potentially pro-inflammatory taxa such as *Prevotella copri*, *Collinsella aerofaciens*, and *Lactobacillus* species has been observed, particularly in early and untreated RA [29].

The phenomenon of molecular mimicry provides a mechanistic link between gut microbes and autoimmunity. Microbial peptides that share structural similarity with host proteins may activate autoreactive T and B cells, leading to cross-reactivity and tissue damage [30]. *Prevotella copri*–derived peptides, for example, have been proposed to mimic joint-associated proteins, triggering immune responses that target synovial tissues.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26jan387

V. GUT MICROBIOTA AS BIOMARKERS FOR RA

The identification of reliable biomarkers for early diagnosis and disease monitoring remains a major challenge in RA. Alterations in gut microbiota composition and function have emerged as promising candidates for biomarker development [31]. Studies have shown that changes in specific bacterial taxa correlate with disease onset, activity, and severity. Increased abundance of *Prevotella copri* and *Lactobacillus salivarius*, along with depletion of *Haemophilus* species, has been associated with early RA and more severe disease.

In addition to microbial composition, microbial metabolites and functional pathways may serve as informative biomarkers. Integration of microbiome data with serological markers such as RF, ACPAs, anti-mutated citrullinated vimentin (anti-MCV), anti-carbamylated protein (anti-CarP) antibodies, and novel proteins such as 14-3-3η may enhance diagnostic accuracy and prognostic stratification [32]. Advanced imaging modalities, including ultrasonography and magnetic resonance imaging, further complement biomarker-based approaches.

VI. EXTRA-ARTICULAR MANIFESTATIONS OF RHEUMATOID ARTHRITIS

RA is increasingly recognized as a systemic disease with diverse extra-articular manifestations that significantly impact morbidity and mortality [33]. Interstitial lung disease affects approximately 10% of RA patients and may precede articular symptoms. Cardiovascular disease represents a major cause of premature mortality in RA, with chronic systemic inflammation accelerating atherosclerosis and increasing the risk of myocardial infarction and stroke [34].

Other extra-articular manifestations include ocular involvement (keratoconjunctivitis sicca, scleritis, episcleritis), hematologic abnormalities (Felty's syndrome), renal complications (secondary amyloidosis), neurological involvement (peripheral neuropathy, cervical spine instability), and cutaneous vasculitis. These manifestations often indicate severe disease and require coordinated multidisciplinary management [35].

VII. MICROBIAL MEDICINE: THERAPEUTIC IMPLICATIONS

The recognition of the gut microbiome as a modifiable factor in RA pathogenesis has opened new avenues for therapeutic intervention. Dietary modification, omega-3 fatty acid supplementation, probiotics, prebiotics, antibiotics, and fecal microbiota transplantation are among the strategies being explored to restore microbial balance and immune homeostasis [36].

Disease-modifying antirheumatic drugs (DMARDs) themselves influence gut microbiota composition. Methotrexate, sulfasalazine, and hydroxychloroquine have been shown to alter specific bacterial populations, potentially contributing to their therapeutic effects. However, non-steroidal anti-inflammatory drugs and antibiotics may disrupt gut integrity and microbial balance, highlighting the need for careful consideration of unintended effects [37].

Recent studies have demonstrated the therapeutic potential of specific commensal bacteria, such as *Prevotella histicola*, which has been shown to suppress inflammatory cytokine production and promote regulatory immune responses in experimental models of arthritis. These findings underscore the heterogeneity within microbial species and the potential for precision microbiome-based therapies [38].

VIII. CONCLUSION AND FUTURE PERSPECTIVES

The intricate interplay between gut microbiota and the immune system has fundamentally transformed our understanding of rheumatoid arthritis [39]. Accumulating evidence suggests that dysbiosis is not merely a consequence of chronic inflammation but may actively contribute to disease initiation, progression, and therapeutic response [40]. While significant advances have been made, many questions remain regarding causality, temporal relationships, and the optimal strategies for microbiome modulation [41].

Future research should focus on longitudinal studies to clarify causal pathways, mechanistic investigations to elucidate microbial–immune interactions, and well-designed clinical trials to evaluate microbiome-targeted therapies [42]. Integrating microbiome data with genetic, immunological, and clinical parameters holds promise for the development of personalized and preventive strategies in RA [43]. Ultimately, a deeper understanding of the gut–joint axis may redefine the prevention, diagnosis, and treatment of rheumatoid arthritis, improving outcomes for millions of patients worldwide [44].

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26jan387

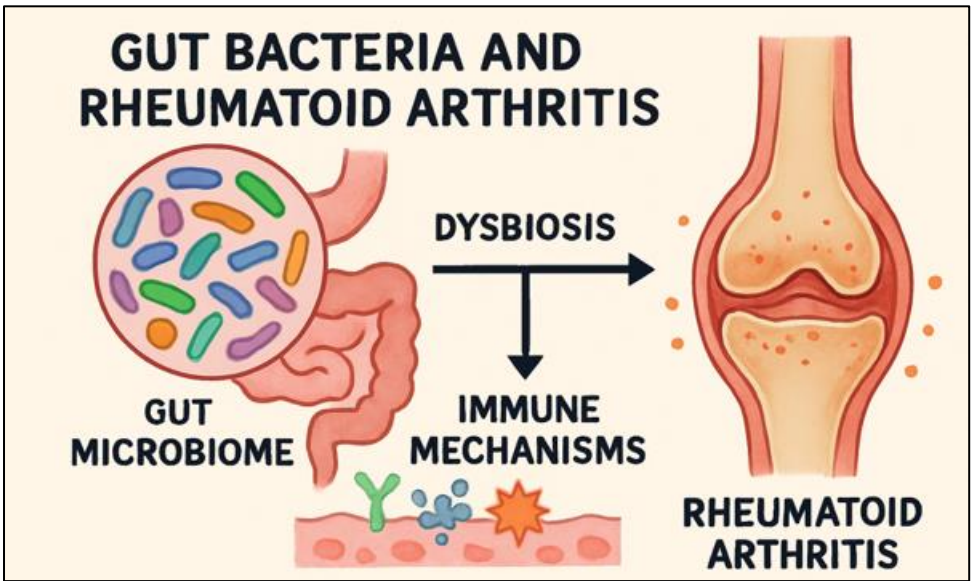

Fig 1: Dysbiosis of the Gut Microbiome Influences Both Local Andemic Immune Mechanisms, Contributing to Rheumatoid Arthritis.

REFERENCES

[1]. 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 Sep 25;5(10):e594-e610. doi: 10.1016/S2665-9913(23)00211-4. PMID: 37795020; PMCID: PMC10546867.

[2]. Ma Y, Chen H, Lv W, Wei S, Zou Y, Li R, Wang J, She W, Yuan L, Tao J, Guo X, Bi S, Tian H, Ma Y, Sun H, Sun C, Xu J, Dong Y, Kang J, Lv H, Zhang M, Jiang Y. Global, regional and national burden of rheumatoid arthritis from 1990 to 2021, with projections of incidence to 2050: a systematic and comprehensive analysis of the Global Burden of Disease study 2021. Biomark Res. 2025 Mar 24;13(1):47. doi: 10.1186/s40364-025- 00760-8. PMID: 40128880; PMCID: PMC11931880.

[3]. Bakinowska E, Stańska W, Kiełbowski K, Szwedkowicz A, Boboryko D, Pawlik A. Gut Dysbiosis and Dietary Interventions in Rheumatoid Arthritis-A Narrative Review. Nutrients. 2024 Sep 23;16(18):3215. doi: 10.3390/nu16183215. PMID: 39339815; PMCID: PMC11435214.

[4]. Wang DW, Pang XT, Zhang H, Gao HX, Leng YF, Chen FQ, Zhang R, Feng Y, Sun ZL. Gut microbial dysbiosis in rheumatoid arthritis: a systematic review protocol of case-control studies. BMJ Open. 2022 Apr 1;12(4): e052021. doi: 10.1136/bmjopen-2021- 052021. PMID: 35365513; PMCID: PMC8977794.

[5]. Scher JU, Sczesnak A, Longman RS, Segata N, Ubeda C, Bielski C, Rostron T, Cerundolo V, Pamer EG, Abramson SB, Huttenhower C, Littman DR. Expansion of intestinal Prevotella copri correlates with enhanced susceptibility to arthritis. Elife. 2013 Nov 5;2: e01202. doi: 10.7554/eLife.01202. PMID: 24192039; PMCID: PMC3816614.

[6]. Pianta A, Arvikar S, Strle K, Drouin EE, Wang Q, Costello CE, Steere AC. Evidence of the Immune Relevance of Prevotella copri, a Gut Microbe, in Patients with Rheumatoid Arthritis. Arthritis Rheumatol. 2017 May;69(5):964-975. doi: 10.1002/art.40003. Epub 2017 Apr 7. PMID: 27863183; PMCID: PMC5406252.

[7]. Maeda Y, Takeda K. Host-microbiota interactions in rheumatoid arthritis. Exp Mol Med. 2019 Dec 11;51(12):1-6. doi: 10.1038/s12276-019-0283-6. PMID: 31827063; PMCID: PMC6906371.

[8]. Su QY, Zhang Y, Qiao D, Song X, Shi Y, Li RQ, et al. Gut microbiota dysbiosis in rheumatoid arthritis: a systematic review and meta-analysis. Explor Med. 2024; 5:709–19.

[9]. Kurkó J, Besenyei T, Laki J, Glant TT, Mikecz K, Szekanecz Z. Genetics of rheumatoid arthritis - a comprehensive review. Clin Rev Allergy Immunol. 2013 Oct;45(2):170-9. doi: 10.1007/s12016-012-8346-7. PMID: 23288628; PMCID: PMC3655138.

[10]. Karami J, Aslani S, Jamshidi A, Garshasbi M, Mahmoudi M. Genetic implications in the pathogenesis of rheumatoid arthritis; an updated review. Gene. 2019 Jun 20; 702:8-16. doi: 10.1016/j.gene.2019.03.033. Epub 2019 Mar 20. PMID: 30904715.

[11]. Terao C, Raychaudhuri S, Gregersen PK. Recent Advances in Defining the Genetic Basis of Rheumatoid Arthritis. Annu Rev Genomics Hum Genet. 2016 Aug 31; 17:273-301. doi: 10.1146/annurev-genom-090314-045919. Epub 2016 May 23. PMID: 27216775; PMCID: PMC6727201.

[12]. Kurkó J, Besenyei T, Laki J, Glant TT, Mikecz K, Szekanecz Z. Genetics of rheumatoid arthritis - a comprehensive review. Clin Rev Allergy Immunol. 2013 Oct;45(2):170-9. doi: 10.1007/s12016-012-8346-7. PMID: 23288628; PMCID: PMC3655138.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26jan387

[13]. Berthelot JM, Darrieutort-Laffite C, Le Goff B. Contribution of HLA DRB1, PTPN22, and CTLA4, to RA dysbiosis. Joint Bone Spine. 2022; 89(6):105446. doi: 10.1016/j.jbspin.2022.105446. Epub 2022 Aug 6. PMID: 35940545.

[14]. Frisell T, Holmqvist M, Källberg H, Klareskog L, Alfredsson L, Askling J. Familial risks and heritability of rheumatoid arthritis: role of rheumatoid factor/anti-citrullinated protein antibody status, number and type of affected relatives, sex, and age. Arthritis Rheum. 2013; 65(11):2773-82. doi: 10.1002/art.38097. PMID: 23897126.

[15]. Wu HJ, Ivanov II, Darce J, Hattori K, Shima T, Umesaki Y, Littman DR, Benoist C, Mathis

[16]. D. Gut-residing segmented filamentous bacteria drive autoimmune arthritis via T helper 17 cells. Immunity. 2010; 32(6):815-27. doi: 10.1016/j.immuni.2010.06.001. PMID: 20620945; PMCID: PMC2904693.

[17]. Flannigan KL, Denning TL. Segmented filamentous bacteria-induced immune responses: a balancing act between host protection and autoimmunity. Immunology. 2018; 154(4):537–46. doi: 10.1111/imm.12950. Epub ahead of print. PMID: 29771448; PMCID: PMC6050222.

[18]. Maeda, Y., Takeda, K. Host–microbiota interactions in rheumatoid arthritis. *Exp Mol Med* **51**, 1–6 (2019). https://doi.org/10.1038/s12276-019-0283-6

[19]. Vivienne Woo, Emily M. Eshleman, Seika Hashimoto-Hill, Jordan Whitt, Shu-en Wu, Laura Engleman, Taylor Rice, Rebekah Karns, Joseph E. Qualls, David B. Haslam, Bruce Vallance, Theresa Alenghat,

[20]. Vaahtovuo J, Munukka E, Korkeamäki M, Luukkainen R, Toivanen P. Fecal microbiota in early rheumatoid arthritis. J Rheumatol. 2008 Aug;35(8):1500-5. Epub 2008. PMID: 18528968.

[21]. Zhao T, Wei Y, Zhu Y, Xie Z, Hai Q, Li Z, Qin D. Gut microbiota and rheumatoid arthritis: From pathogenesis to novel therapeutic opportunities. Front Immunol.; 13:1007165. doi: 10.3389/fimmu.2022.1007165. PMID: 36159786; PMCID: PMC9499173.

[22]. Maeda, Y., Takeda, K. Host–microbiota interactions in rheumatoid arthritis. *Exp Mol Med* **51**, 1–6 (2019). https://doi.org/10.1038/s12276-019-0283-6

[23]. Zhang, X., *et al.* (2015). The oral and gut microbiomes are perturbed in rheumatoid arthritis and partly normalized after treatment. *Nature Medicine, 21*(8), 895–905. https://doi.org/10.1038/nm.3914

[24]. Liu, X., *et al.* (2016). Role of the gut microbiome in modulating arthritis progression in mice. *Scientific Reports, 6*, 30594. https://doi.org/10.1038/srep30594

[25]. Zhao T, Wei Y, Zhu Y, Xie Z, Hai Q, Li Z, Qin D. Gut microbiota and rheumatoid arthritis: From pathogenesis to novel therapeutic opportunities. Front Immunol. 2022; 13:1007165. doi: 10.3389/fimmu.2022.1007165. PMID: 36159786; PMCID: PMC9499173.

[26]. Maeda Y, Takeda K. Host-microbiota interactions in rheumatoid arthritis. Exp Mol Med. 2019; 51(12):1-6. doi: 10.1038/s12276-019-0283-6. PMID: 31827063; PMCID: PMC6906371.

[27]. Chen, B., *et al.* (2021). The key role of gut microbiota in the pathogenesis and treatment of rheumatoid arthritis. *Frontiers in Pharmacology, 12*, 626396. https://doi.org/10.3389/fphar.2021.626396

[28]. Smolen, J. S., *et al.* (2018). Rheumatoid arthritis. *Nature Reviews Disease Primers, 4*(1), 18001. https://doi.org/10.1038/s41572-018-0050-3.

[29]. O'Dwyer, D. N., & Long, J. (2019). *Rheumatoid arthritis-associated interstitial lung disease: prevalence, pathogenesis and outcomes. The Journal of Rheumatology, 46*(4), 360–367

[30]. Smolen, J. S., Aletaha, D., Barton, A., et al. (2018). *Rheumatoid arthritis. Nature Reviews Disease Primers, 4*, 18001. doi:10.1038/s41572-018-0050-3

[31]. Patel R, Killeen RB, Akhondi H. Felty Syndrome. In: StatPearls. Treasure Island (FL): StatPearls

[32]. Reddy AK, Kolfenbach JR, Palestine AG. Ocular manifestations of rheumatoid arthritis. Curr Opin Ophthalmol. 2022 Nov 1;33(6):551-556. doi: 10.1097/ICU.0000000000000890. Epub 2022. PMID: 36165413.

[33]. Galor A, Thorne JE. Scleritis and peripheral ulcerative keratitis. Rheum Dis Clin North Am. 2007; 33(4):835-54, vii. doi: 10.1016/j.rdc.2007.08.002. PMID: 18037120; PMCID: PMC2212596.

[34]. Fraenkel, L., Bathon, J. M., England, B. R., St. Clair, E. W., Arayssi, T., Carandang, K., Deane, K. D., … Sparks, J. A. (2021). *2021 American College of Rheumatology guideline for the treatment of rheumatoid arthritis*. *Arthritis Care & Research, 73*(7), 924–939. https://doi.org/10.1002/acr.24596

[35]. Clemente, J. C., Ursell, L. K., Parfrey, L. W., & Knight, R. (2012). The impact of the gut microbiota on human health: an integrative view. *Cell, 148*(6), 1258–1270. https://doi.org/10.1016/j.cell.2012.01.035

[36]. Wallace, T. C., & Miles, E. A. (2014). Omega-3 polyunsaturated fatty acids and their role in immune function, nutrition, and health. *American Journal of Clinical Nutrition, 100*(1), 348S–354S. https://doi.org/10.3945/ajcn.114.083978

[37]. Zhu, C., Song, H., Chen, Q., Liu, Z., & Wu, S. (2018). Methotrexate alters gut microbiota in rheumatoid arthritis patients. *Clinical Rheumatology, 37*(1), 123–130. https://doi.org/10.1007/s10067-017-3805-2

[38]. Mai, V., & Greenwald, B. (2007). Sulfasalazine and the gut microbiota in RA.

[39]. *Inflammopharmacology, 15*(5), 157–162. https://doi.org/10.1007/s10787-007-0004-3

[40]. Johnson, E. E., & Smith, R. D. (2019). Hydroxychloroquine and gut microbiome modulation. *Journal of Antimicrobial Chemotherapy, 74*(12), 3473–3480. https://doi.org/10.1093/jac/dkz348

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26jan387

[41]. Zhang, X., Zhang, D., Jia, H., Feng, Q., Wang, D., Liang, D., & Li, J. (2015). *Nature Medicine*, *21*(8), 895–905. https://doi.org/10.1038/nm.3914
[42]. Schnitzer, T., et al. (2016). Impact of NSAIDs on intestinal microbiota: protective roles of probiotics. *Gastroenterology*, *150*(2), S639. https://doi.org/10.1053/j.gastro.2015.12.723
[43]. Huang, R., Ning, Z., Yang, F., & Wang, W. (2020). Effects of *Bifidobacterium*, *Lactobacillus*, and *Faecalibacterium prausnitzii* in inflammation models. *Frontiers in Immunology*, *11*, 619356. https://doi.org/10.3389/fimmu.2020.619356
[44]. Manfredo Vieira, S., Hiltensperger, M., Kumar, V., Zegarra-Ruiz, D., Dehner, C., Khan, N. & Kriegel, M. A. (2018). *Science*, *359*(6380), 1156–1161. https://doi.org/10.1126/science.aar7201
[45]. Mueller AL, Payandeh Z, Mohammadkhani N, Mubarak SMH, Zakeri A, Alagheband Bahrami A, Brockmueller A, Shakibaei M. Recent Advances in Understanding the Pathogenesis of Rheumatoid Arthritis: New Treatment Strategies. Cells. 2021; 10(11):3017. doi: 10.3390/cells10113017. PMID: 34831240; PMCID: PMC8616543.
[46]. Shan L, Chelliah R, Rahman SME, Hwan Oh D. Unraveling the gut microbiota's role in Rheumatoid arthritis: dietary pathways to modulation and therapeutic potential. Crit Rev Food Sci Nutr. 2025; 65(17):3291-3301. doi: 10.1080/10408398.2024.2362412. 2024. PMID: 38832654.