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Review Article

Exploring the Potential of Probiotics and Gut Microbiota Modulation in the Management of Rheumatoid Arthritis: A Review of Current Mechanisms and Therapeutic Strategies

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Abstract

Summary: Background: Rheumatoid arthritis (RA) is a persistent autoimmune disorder that attacks the joints, resulting in inflammation and potential joint deterioration over time. This disease impacts roughly 1% of the global population, occurs more frequently in women, and arises from both inherited and environmental factors.

Main Body: Even though disease-modifying antirheumatic drugs (DMARDs) and nonsteroidal anti-inflammatory drugs (NSAIDs) are widely available, their effectiveness is often hampered by side effects, toxicity concerns, and high costs. Researchers are increasingly focusing on the pre-clinical phase of rheumatoid arthritis (RA) as a key opportunity for intervention. Growing evidence underscores the gut microbiome's pivotal influence on RA's onset. An imbalance in gut bacteria—known as dysbiosis—appears to trigger autoimmunity in conditions like RA, possibly via molecular mimicry and other pathways that fuel immune overreactions.

Probiotics, especially strains from *Lactobacillus* and *Bifidobacterium*, offer hope by restoring gut balance, dialing down inflammation, and easing RA symptoms. Both animal models and human trials back this up, showing drops in inflammatory markers like pro-inflammatory cytokines and C-reactive protein (CRP), alongside real-world relief from issues such as swollen joints and pain.

Conclusion: This review explores how gut microbes contribute to the development of rheumatoid arthritis (RA) and highlights the encouraging potential of probiotics for easing RA symptoms. On top of that, dietary strategies—like the Mediterranean diet, which can reshape the gut microbiome—hold promise for better RA control by curbing inflammation and boosting overall disease outcomes.

Keywords: Rheumatoid arthritis, gut microbiota, probiotics, *Lactobacillus*, *Bifidobacterium*.

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disorder that sparks widespread inflammation. It primarily targets the joints, triggering nonsuppurative proliferative synovitis that often progresses to joint fusion and breakdown of articular cartilage. Beyond the joints, RA can affect various tissues and organs, such as the skin, heart, lungs, blood vessels, and muscles ². While joints and tendons show large pathological changes, extra-articular issues occur less often. Women face 2-3 times higher risk than men, with RA touching about 1% of people worldwide ². Though its exact cause remains elusive, experts believe environmental and genetic factors team up to ignite an aberrant autoimmune reaction ³.

Clinicians often turn to two key drug types for managing rheumatoid arthritis: disease-modifying antirheumatic drugs (DMARDs) and nonsteroidal anti-inflammatory drugs (NSAIDs) ⁴. That said, NSAIDs and DMARDs have limitations, including side effects, risks of toxicity, and high costs ⁵.

Fig.1 shows a healthy joint i.e. smooth, cushioned cartilage, versus RA: eroded bone, swollen synovium, worn padding, tight space causing pain and stiffness. Researchers see the pre-clinical stage of RA as a key opportunity for intervention, where kicking off treatment before clinical symptoms appear could ward off major joint damage seen on X-rays and help secure lasting remission ⁶.

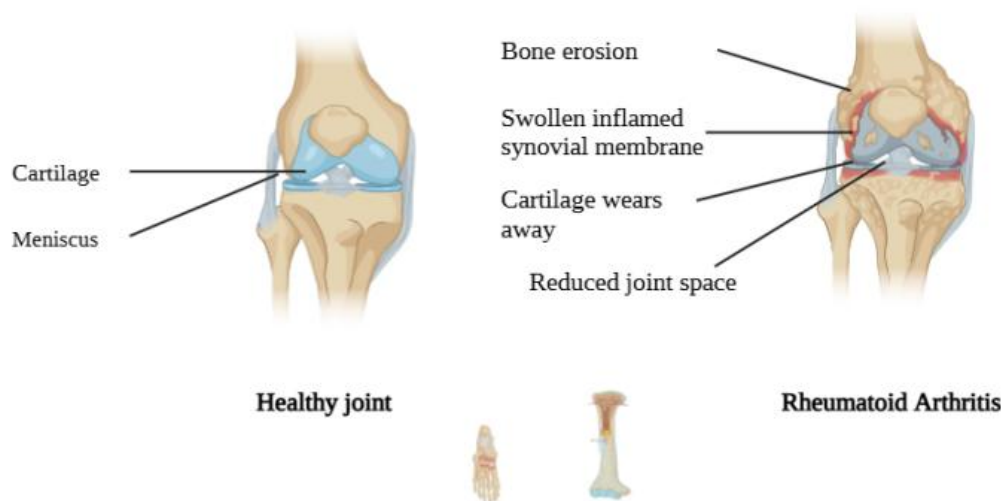


Figure 1: The joint's structure and its modifications in rheumatoid arthritis ⁶.

Pre-clinical RA represents an at-risk state that comes before clinical arthritis and full-blown RA ⁷. It often involves a breakdown in immune tolerance, leading to autoantibodies like those targeting rheumatoid factor or citrullinated proteins ⁸. A wealth of studies in humans and mouse models highlights the gut microbiota's central role in driving this early phase (Table 1). Past work suggests gut dysbiosis disrupts immune self-

tolerance and speeds RA progression, partly through molecular mimicry ⁹. In particular, peptides from gut bacteria can mimic RA autoantigens, sparking cross-reactive autoantibodies that attack joint cartilage ¹⁰. As shown in Fig.2, multi-omics analyses of the microbiome and its metabolites show these gut-derived compounds act as immunomodulators, influencing immune cell development and function.

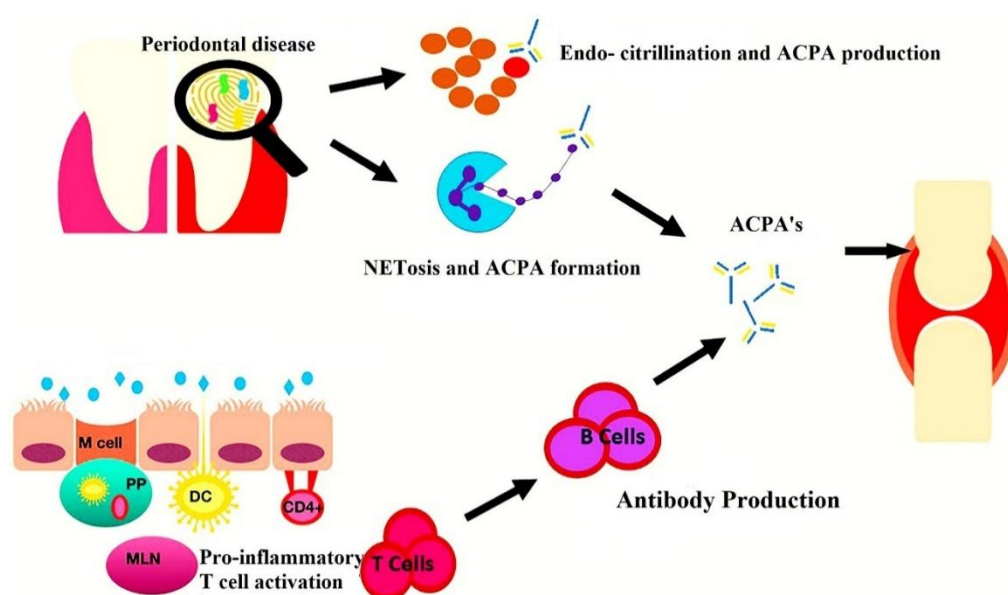


Figure 2: Depiction of the role of the oral and gut microbiomes on RA ¹¹.

Probiotics boost health by ramping up beneficial gut bacteria. Strains like *Lactobacillus* and *Bifidobacterium*—naturally present in our bodies—show up in foods or supplements. Each person hosts a unique microbial community across sites like the mouth, skin, and intestines ¹².

Probiotics appear to work through three main mechanisms:

- Curbing harmful bacteria linked to allergies and infections.

- Balancing "good" and "bad" microbes in the body.
- Restocking healthy ones depleted by illness.

Lactobacillus and *Bifidobacterium* stand out as top probiotics, with well-documented perks such as:

- Easing gas and bloating.
- Warding off or softening colds and flu.
- Lowering blood pressure.
- Relieving inflammatory bowel conditions like Crohn's disease and ulcerative colitis.

- Accelerating recovery from certain gut infections.

Probiotics hold real potential for people with inflammatory arthritis¹³. These beneficial microbes seem to aid treatment by lowering C-reactive protein (CRP), a key inflammation marker. RA patients often deal with gut lining inflammation too, which ramps up intestinal motility¹⁴. That breach lets certain bacteria slip through the intestinal wall into the bloodstream, triggering systemic infections. Probiotics shine by calming gut immune overreactions, fortifying the intestinal barrier, and tackling widespread permeability issues alongside microbiome shifts. They're especially useful for conditions with weakened mucosal defenses, like viral infections or pro-inflammatory disorders¹⁵. Overall, these supplements can team up to protect joints and bolster whole-body health. A recent journal study split 46 RA patients into two groups: one got daily *Lactobacillus casei* supplements, the other a placebo. Researchers found this probiotic approach could serve as a valuable add-on therapy for RA¹⁶.

Pathophysiology of Rheumatoid Arthritis and the mechanisms of Probiotics

Interactions among the immune system, gut bacteria, and intestinal lining spark the widespread inflammation seen in RA. A core driver is the imbalance of pro-inflammatory cytokines like TNF, IL-1 β , IFN- γ , IL-6, IL-12, and IL-17, which fuel the disease's destructive processes. Along the gut-joint axis in inflammatory arthritis, leaky gut walls expose the immune system to

microbes, igniting a body-wide response that zeroes in on the joints with local inflammation¹⁷.

Probiotics offer a practical way to fix gut dysbiosis and dial back the inflammatory cytokine storm tied to arthritis. Disrupted gut microbiota likely plays a pivotal role in kickstarting RA pathology¹⁸.

Probiotics ramp up regulatory cytokines in the gut via tolerogenic dendritic cells (DCs) or Tregs. These cytokines travel to target organs, boosting Tregs that home in on inflamed sites. Probiotic byproducts like short-chain fatty acids (SCFAs) also curb systemic inflammation and tweak immune responses by shaping immune cell activity. SCFAs fine-tune leukocyte functions, including eicosanoid and chemokine production—and promote anti-inflammatory cytokines such as TNF, IL-2, IL-6, and IL-10 (Fig.3.)¹⁹.

On top of that, probiotics and their metabolites strike a balance: fending off pathogenic bacteria invasion, adhesion, and spread while tolerating normal gut flora. This could help seal leaky gut walls, a key feature of the gut-joint axis in inflammatory arthritis.

Research also reveals that *L. casei* can dial down pro-inflammatory cytokines and ease RA symptoms in patients on disease-modifying antirheumatic drugs (DMARDs), pointing to a helpful synergy between the two.

In short, probiotics like these may tame RA's inflammatory drive by balancing cytokine production, strengthening the gut barrier, and teaming up effectively with DMARDs.

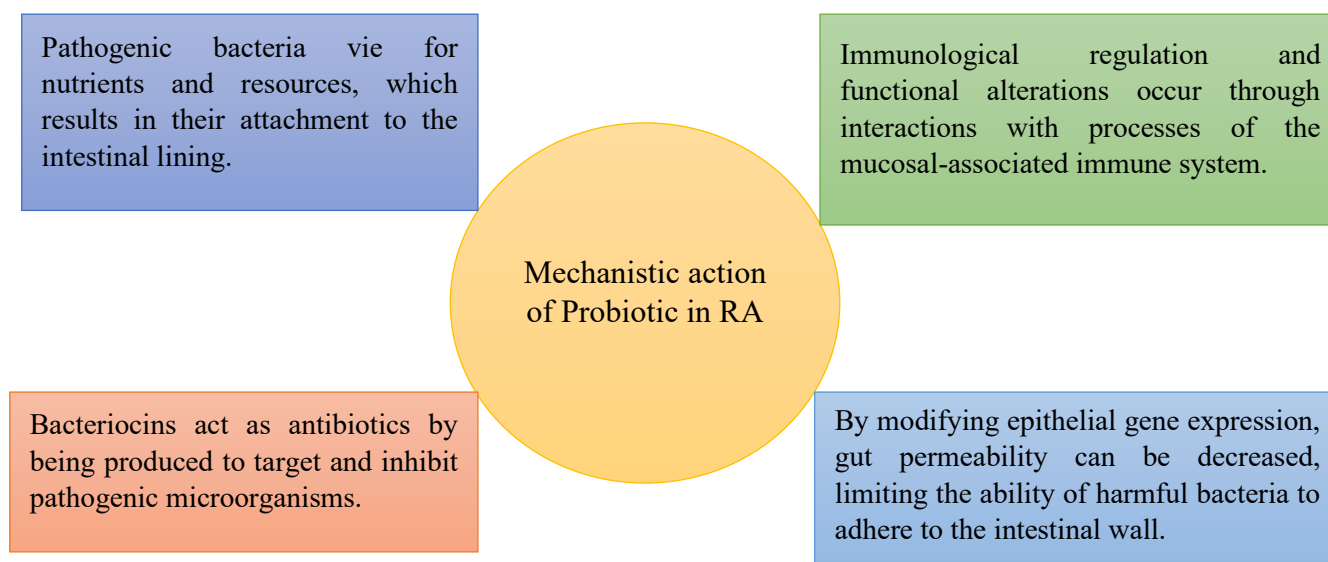


Figure 3: Mechanism of Probiotic in RA¹⁹.

Table 1: List of research studies on the therapeutic effects of probiotics in humans and animals.

Probiotics	Period	Study Framework	Main Findings	Ref
Lactobacillus casei ATCC 334	28Days (2×10^8 CFU/ml)	Preclinical trial	Histopathological examination revealed normal synovial membrane and cartilage, without any signs of bone destruction. The arthritis showed decreased severity, along with lower levels of pro-inflammatory cytokines.	20
Lactobacillus casei ATCC 334	30 days (2×10^8 CFU/day)	Preclinical trial	Joints exhibited less swelling, milder arthritis, and reduced bone damage. Correction of dysbiosis in the gut microbiota	21
Lactobacillus casei	12 weeks (4×10^8 CFU/G)	Preclinical trial	Clinical symptoms improved notably, with less paw swelling, reduced lymphocyte infiltration, and diminished cartilage destruction. A rise in the levels of anti-inflammatory cytokines (IL-10 and TGF- β) A reduction in pro-inflammatory cytokines CII-reactive T cell proliferation dropped, along with lower levels of Th1-type IgG isotypes (IgG2a and IgG2b).	22
Lactobacillus plantarum MTCC No. 1047	21 days (10^5 , 10^7 , 10^9 CFU/ animal)	Rat model of arthritis induced by Complete Freund's adjuvant (CFA)	Suppression of the release of inflammatory markers such as CRP, ESR, RF, and TNF- α Improvement in the arthritic index, joint stiffness, gait performance, and mobility assessment	23
Lactobacillus casei 01	8 weeks (10^8 CFU/day)	RCT with a double-blind protocol In Iran 46 RA patients	Reduction in SOD and GPx enzyme activity	24
Lactobacillus casei 01	8 weeks (10^8 CFU/day)	RCT with a double-blind protocol A group of 45 rheumatoid arthritis (RA) patients in Germany, aged between 20 and 80, with a disease duration of over one year.	Reduction in serum hs-CRP levels, tender and swollen joint counts, GH score, and DAS28 index A notable difference was found between the L. casei 01 and placebo groups in IL-10, IL-12, and TNF- α levels.	25
Lactobacillus rhamnosus GG (LGG)	12 Months (5×10^9 CFU/ capsule, 2 capsule/ Day)	clinical trial with a double-blind A group of 21 rheumatoid arthritis (RA) patients in Finland,	Reduction in the average number of tender and swollen joints, as well as RA activity A slight rise in serum IL-1 β .	26

		aged between 18 and 64, with a disease duration of at least one year.		
Lactobacillus acidophilus, Lactobacillus casei Bifidobacterium bifidum	8 week (2*10 ⁹ CFU/g each)	A randomized, double-blind, placebo-controlled study In Iran 54 patients with RA at the age of 25-70	Serum hs-CRP levels, insulin values, HOMA-IR, and HOMA-B all decreased. A rise in plasma NO, plasma glutathione, DAS-28, and VAS pain.	27
Lactobacillus acidophilus La-14, Lactobacillus casei Lc-11, Lactobacillus Lactis	60 days (10 ⁹ CFU/g each)	A randomized and double blind placebo-controlled study. In Brazil 42 RA patients	A lowering in white blood cell count and TNF- α and IL-6 plasma levels. A decrease in NO metabolites and an increase in sulfhydryl groups and total antioxidant capacity for radical trapping.	28

Microbiome-induced molecular mimicry in Rheumatoid Arthritis

We've long known about molecular mimicry, but lately, eyes are turning to how our resident microbes pull it off. As per Table 2, studies show human-associated bacteria churn out proteins strikingly similar to our own. In certain cases, this resemblance throws the immune system off balance, potentially sparking autoimmune diseases ²⁹.

Citrullination—a normal bodily process—plays roles in key functions like cell death, final cell maturation, gene regulation, and reproductive growth ³¹. The enzyme PAD drives this by modifying various RA-linked autoantigens, such as vimentin, fibrinogen, enolase, and even proteins from *P. gingivalis*. Studies also confirm anti-CCP antibodies in RA patients ³².

Table 2: Microbiome-induced molecular mimicry in Rheumatoid Arthritis

Microbiome	Immune response	Stage of RA	Ref.
Bacteroidaceae, Lachnospiraceae, and S24-7	Elevated IL-17 levels in serum, along with a higher CD8+ T cell-to-Th17 ratio in the spleen; The spleen shows fewer dendritic cells, B cells, and Tregs.	The progression of RA	33
Haemophilus spp., Lactobacillus salivarius	Serum anti-CCP, RF, CRP, IgG and DAS28 levels were elevated.	Established RA	34
Prevotellacopri	The number of intestinal Th17 cells was increased; IL-17 levels were high in regional lymph nodes and lymph glands.	Early RA	35
Aggregatibacter actinomycetem comitans	Host neutrophils showed excessive citrullination, driven by dysregulated activation of citrullinating enzymes.	Pre-clinical RA	36
Anaeroglobusgeminatus	The presence of ACPAs/ rheumatoid factor was observed.	New onset RA	37
Crypto bacterium curtum	Large amount of citrulline were produced.	Established RA	38
Defluviitaleaceae_UGC-011, Neisseriaoralis, Prevotella_6	Serum tests revealed positive ACPA titers, with elevated levels of immunoglobulin G (IgG), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR).	Pre-clinical RA.	39

Gut Microbiota Modulation by Mediterranean Diet in Rheumatoid Arthritis

Environmental factors, not genetics, mainly reshape gut microbiota makeup. Diet stands out as a top influencer of this microbial balance. Experts increasingly view nutrition's power to tweak gut bacteria as a smart way to treat and prevent diseases like RA⁴⁰. Plenty of studies probe how n-3 PUFAs affect RA symptoms⁴¹. Boosting intake of EPA and DHA packs them into cell membranes, bumping out arachidonic acid (AA) from immune cell phospholipids⁴². These fatty acids fuel pro-resolving mediators that help dial down inflammation and restore balance, curbing the cell's inflammatory bent⁴⁴. Many studies confirm n-3 PUFAs improve other RA symptoms too, such as fewer tender joints (TJ) and swollen joints (SJ), plus shorter morning stiffness (MS)⁴⁵. A meta-analysis by Gioxari et al. found that taking n-3 PUFAs by mouth significantly eased MS duration, TJ counts, erythrocyte sedimentation rate (ESR), and pain scores on visual scales⁴⁶.

Patients needed fewer nonsteroidal anti-inflammatory drugs (NSAIDs) compared to placebo. Even with strong evidence for n-3 PUFAs in RA, studies suffer from inconsistencies in dosing, duration, and placebo choices⁴⁷. RA patients seem to need at least 3g daily of EPA and DHA for 12 weeks or more to see meaningful drops in pain scores. One study showed that after 12 weeks on a Cretan Mediterranean diet (MD), RA patients with stable, low disease activity gained clear benefits in DAS-28 scores, HAQ, and two Short Form-36 measures⁴⁸.

That study had some limitations, though: a small sample size, baseline DAS-28 scores as high as 7 (signaling active disease), significant BMI differences between groups, and no long-term follow-up beyond 12 weeks⁵¹.

In another trial, McKellar et al. tested written guides versus cooking classes to promote the Mediterranean diet (MD) in women with RA. Over three months, the workshop group boosted their intake of fruits, vegetables, and legumes while shifting from saturated to monounsaturated fats⁵². Compared to controls, they saw big gains in patient global assessment (PGA) at six months, pain scores at three and six months, morning stiffness (MS) at six months, and HAQ at three months⁵³. This suggests stronger MD education leads to better results. Still, despite statistical wins, DAS-28 barely budged with modest changes overall—so larger studies are needed to confirm⁵¹.

Conclusion

Rheumatoid arthritis (RA) continues to puzzle researchers as a tough autoimmune condition shaped by genetic, environmental, and immune triggers. One exciting frontier? The gut microbiome and probiotics, which show real potential in both sparking RA and helping control it. Through tricks like molecular mimicry and tweaking immune responses, gut bacteria drive disease onset and advance—particularly before symptoms fully hit.

Strains like *Lactobacillus* and *Bifidobacterium* make probiotics a hopeful add-on for RA care. They restore

gut balance, tighten up leaky intestines, ease body-wide inflammation, and fine-tune immune activity. Clinical and animal studies back this, showing drops in symptoms, inflammatory signals, and even teamwork with standard DMARDs.

That said, promising early data calls for bigger, rigorous trials to confirm real-world benefits and safety over time. Weaving in probiotics and gut-focused tweaks could offer RA patients a fresh, affordable, gentler option—boosting daily life and lightening the disease's load.

List of Abbreviations

RA: Rheumatoid arthritis

NSAID: Non-steroidal anti-inflammatory drug

DMARDs: Disease-modifying antirheumatic drugs

CRP: C-reactive protein

COX: Cyclooxygenase

PPAD: *Porphyromonas gingivalis* peptidylarginine deiminase (PPAD)

PAD: Peptidyl arginine deiminase (PAD)

HAQ: Health Assessment Questionnaire

MD: Mediterranean diet

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1. Ms. Snehal A Gojare- Conceptualization & Guidance
2. Ms. Pranoti Aher- Literature Searching
3. Ms. Rachana Lokhande- Literature Searching
4. Ms. Nikita Game -Paper writing & editing
5. Ms Priyanka N Khamkar- Paper writing & editing

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