Natural compounds for the treatment of rheumatoid arthritis based on the 'gut-joint axis' (Review)

WENJIE HU, RUI LI and ZHONGMING ZHANG

Department of Internal Medicine, Chengdu Xindu District Second People's Hospital, Chengdu, Sichuan 610501, P.R. China

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Abstract. Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease whose etiology remains incompletely understood. As the proposal and progress of the 'mucosal origin hypothesis', the role of the 'gut-joint axis' mechanism in the pathological process of RA is gradually being revealed. Changes in the intestinal microbiota, damage to the mucosal barrier, mucosal immune dysfunction and disorders of microbial-derived metabolites all regulate the occurrence and development of RA. Natural compounds, bioactive entities isolated from natural sources, have demonstrated distinct therapeutic advantages across a broad spectrum of diseases. The intestine may be the key for these compounds to exert their therapeutic effects on diseases. The present review summarized the 'gut-joint axis' in RA and the natural compounds that exert therapeutic effects via this pathway. It emphasized that improving intestinal microecology may be a potential treatment method for RA, and natural compounds are expected to become promising treatment strategies for RA in this way. However, there are still numerous problems that need to be urgently solved to complete the clinical transformation of these natural compounds.

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Correspondence to: Dr Rui Li, Department of Internal Medicine, Chengdu Xindu District Second People's Hospital, 99 Fanjin Road, Xinfan, Xindu, Chengdu, Sichuan 610501, P.R. China
E-mail: 286858632@qq.com

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1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disorder primarily characterized by symmetrical, multi-joint pain and swelling, often accompanied by local joint destruction. The underlying pathogenesis remains incompletely understood, but it involves a complex interplay of genetic, environmental, and immune factors, ultimately leading to the breakdown of immune tolerance and systemic immune dysregulation (1). RA markedly impairs the quality of life of patients. Over the past three decades, its global prevalence has steadily increased, with the 2020 RA Global Burden of Disease Study reporting an estimated prevalence of ~0.2%, placing a substantial burden on the global economy (2).

Despite significant advances in the treatment of RA, outcomes remain unsatisfactory. Due to its complex pathogenesis, no drug or therapy can fully halt RA progression, and most treatments are associated with notable side effects (3). Epidemiological and translational studies have increasingly emphasized the critical role of mucosal interactions with symbiotic bacteria in RA development (4-6). Research on high-risk RA populations has revealed lung mucosal inflammation, as well as the production of local anti-citrullinated protein antibodies (ACPAs) and rheumatoid factor, supporting the 'mucosal origin hypothesis' (7,8). Further investigations have identified distinct mucosal mechanisms, including those of the intestinal mucosa, that drive RA progression (9). The intestine, home to the largest concentration of innate and adaptive immune cells, forms a vital interface between the internal environment and external factors, linking environmental influences to systemic immunity (10,11). Alterations in the gut microbiota, which may respond to external environmental and changes or be driven by systemic inflammation can occur before the onset of arthritis. Emerging research increasingly highlights the critical role of the 'gut-joint axis' in the transition from preclinical to clinical RA.

The relationship between intestinal microecological imbalance and RA involves complex physiological and pathological mechanisms. Studies from RA animal models and preclinical RA (PreRA) populations indicate that gut alterations may precede the onset of the disease and potentially serve as latent triggers of systemic inflammation (12-16). Conversely, a reverse 'gut-joint axis' mechanism may also exist, although further research is required to substantiate this hypothesis. For example, increasing levels of inflammatory factors in the

joints may spread peripherally, contributing to or exacerbating damage to the intestinal mucosal barrier and microbiota dysbiosis (17,18). Additionally, pain may alter the metabolic products of gut microbiota and intestinal hormones (19,20). The present review summarized the 'gut-joint axis' mechanism in RA, highlighting changes in gut microbiota, interactions between microbiota and genetic risks, alterations in intestinal permeability, dysregulated mucosal immune responses, molecular mimicry, disruption of microbial-derived metabolites, gut hormone regulation and sex bias. These factors, alone or in combination, contribute to the onset and progression of RA (Fig. 1).

Natural compounds, biologically active substances derived from natural sources, have garnered significant attention due to their diverse biological effects, including antioxidant, anti-inflammatory, anti-fibrotic, anti-tumor and anti-angiogenesis properties. Given the limitations of current RA treatments, the present review explored several natural compounds that exert anti-RA effects through the 'gut-joint axis' mechanism, offering new insights and potential strategies for innovative RA therapies (Fig. 2).

2. Methods

The present review conducted a systematic literature search across PubMed (https://pubmed.ncbi.nlm.nih.gov; version: Baseline 2025 released December 2024), Web of Science (https://www.webofscience.com; version: 2025-09 weekly update), SpringerLink (https://link.springer.com; version: Content release 2025.09), ScienceDirect (https://www.sciencedirect.com; version: 2025 issue 10), ACS Publications (https://pubs.acs.org; version: 2025 volume 147), Wiley Online Library (https://onlinelibrary.wiley.com; version: 2025 volume releases) and CNKI (https://www.cnki.net; version: CNKI 2025 Master Release) for studies published between January 1995 and September 2025. The following keywords were used: 'Rheumatoid Arthritis', 'Gut', 'Natural compounds', 'Alkaloids', 'Polyphenols', 'Polysaccharides', 'Glycosides', 'Flavonoids', 'Terpenoids', 'CD4$^+$T cells' and 'Hormone'. Pending clinical trials were retrieved from ClinicalTrials.gov and the Center for Drug Evaluation (http://www.cde.org.cn; version: 2025 Master Release), National Medical Products Administration (https://www.nmpa.gov.cn; version: 2025 Master Release). Studies included were clinical studies, laboratory studies (including animal studies or *in vitro* cellular studies, or combined animal and *in vitro* studies), meta-analyses and bioinformatics studies, irrespective of language. Exclusion criteria were: i) Duplicate publications; ii) clinical trials lacking relevant data; iii) newspapers, conference proceedings, commentaries, and non-experimental information; iv) low-quality studies or those making erroneous conclusions; and v) retention of multiple reports on the same topic for comparison and discussion.

3. The 'gut-joint' axis mechanism of RA

Changes in the intestinal microbiota. The gut microbiota plays a pivotal role in regulating host immunity and influencing the progression of RA through various mechanisms (21,22). Several recurring patterns have been identified in the intestinal microbiota of patients with RA, including an increase in the abundance of *Prevotella* and *Lactobacillus* and a decrease in *Faecalibacterium* and *Bacteroidetes* (14,23-27). Among these, the pathogenic role of *Prevotella* in RA has been extensively studied. *Prevotella* is closely associated with the RA risk gene human leukocyte antigen (*HLA*)-*DRB1* and is involved in the disease's adaptive immune response (12). Notably, antibodies against *Prevotella copri (P. copri)* are specific to patients with RA, with antibody levels to other symbiotic bacteria in patients with RA are similar or lower compared with those in other patients with arthritis or healthy controls (28,29). Moreover, when *P. copri* enters the systemic circulation, it can selectively accumulate in the joints, potentially inducing synovial hyperplasia and deformation by promoting synovial tissue growth (30). *P. copri* is one of several intestinal microbiota species with pathogenic effects on RA and their mechanisms have been comprehensively reviewed (31,32).

The interaction between the gut microbiota and genetic risk. Genome-wide association studies have identified several RA susceptibility alleles, including *HLA-DRB1*, *PTPN22*, and *PADI4* genes (33,34). Alleles within the class II loci of *HLA*, particularly those in *DRB1*, show a strong association with RA risk in individuals positive for autoantibodies, with >70% of ACPA-positive patients with RA carrying the *HLA-DRB1* allele (35). Environmental factors may serve as significant triggers for individuals with a genetic predisposition to develop RA. Notable microbiome changes have been observed in the intestines of healthy individuals carrying the RA risk allele *HLA-DRB1*, including an increase in *Lachnospiraceae*, *Clostridiaceae* and *Bifidobacterium longum* species (36). Wells *et al* (12) classified *Prevotella* species based on predicted types and assigned numerical names according to the SILVA database. The authors cohort study found that, even in the absence of clinically detectable disease, the genetic risk of RA was associated with specific gut microbiota. The *Prevotella_7* strain (whose predicted type remains uncertain) was particularly strongly linked to the RA genotype.

Increased intestinal permeability. The intestine plays a critical role as a conduit between the body's internal environment and external factors. When the intestinal mucosal barrier is compromised, non-self antigens can penetrate and invade the body, triggering and exacerbating systemic inflammatory responses. This can lead to the breakdown of self-immune tolerance and the disruption of immune homeostasis (37). Additionally, increased intestinal permeability allows immune cells to migrate beyond the intestine, potentially causing extraintestinal inflammation (38,39). Clinical studies have shown that intestinal permeability is elevated in both preclinical and established patients with RA (24,39-42). Individuals with high zonulin levels (>10 ng/ml) during the early stages of RA are at greater risk of developing the disease within a year (39). Furthermore, persistent arthritis may further compromise intestinal permeability, facilitating the invasion of joint synovial fluid by intestinal microorganisms in the IV stage of RA (17). In *vitro* studies have also indicated that intestinal bacteria from PreRA subjects directly modulate the expression of zonula occludens-1 in Caco-2 cells at both the transcriptional and protein levels (5). *Collinsella*, a genus

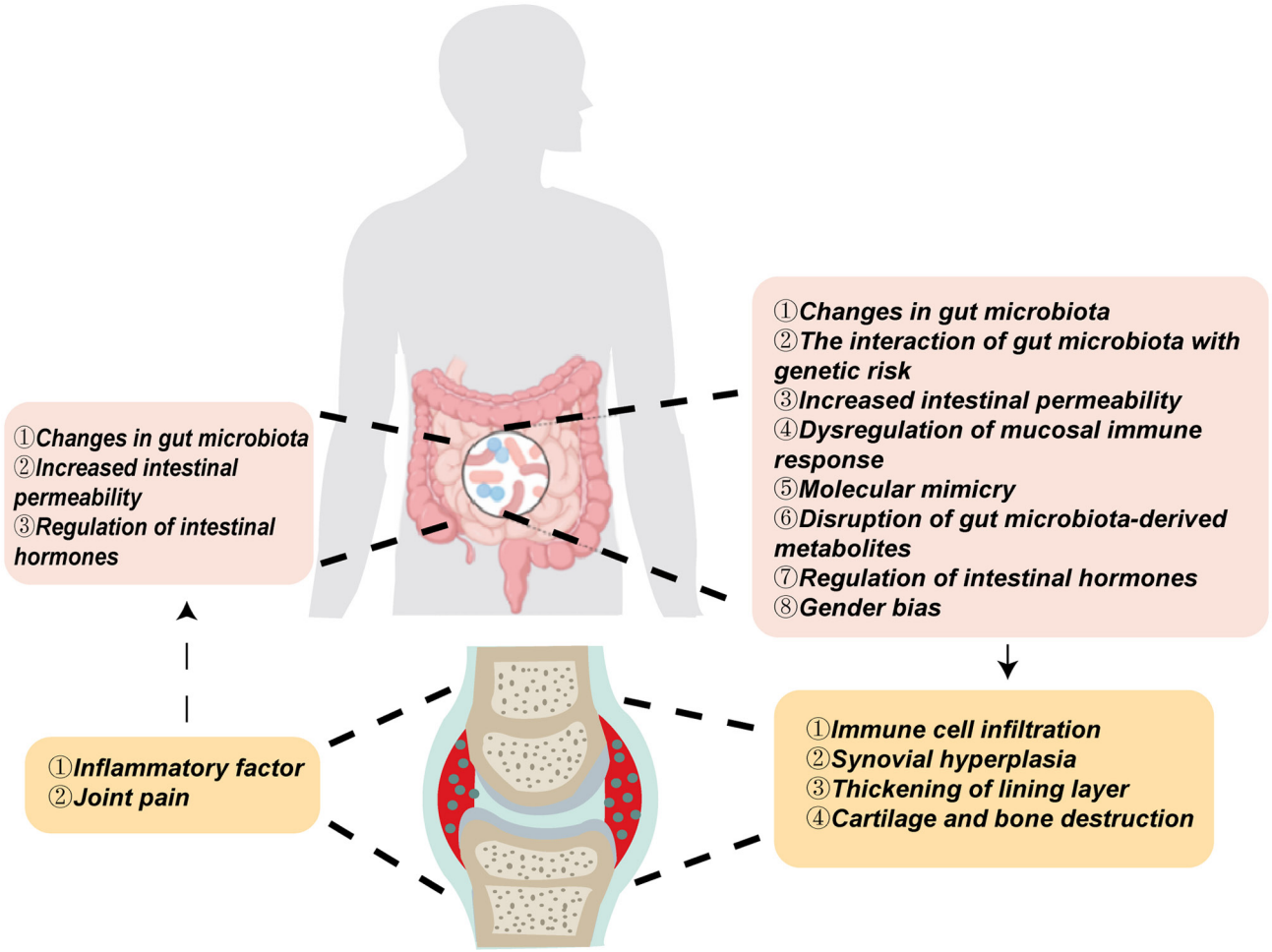

Figure 1. The 'gut-joint axis' mechanism in RA. Changes in the gut, such as the microbiota and mucosal permeability, may be potential mechanisms that promote the occurrence and progression of RA. RA, rheumatoid arthritis.

within the Actinobacteria phylum, is markedly enriched in the gut microbiota of patients with RA. Its overgrowth disrupts intestinal barrier function and is independently associated with disease-related inflammatory activity (14,43). In collagen-induced arthritis (CIA) mice, serum zonulin levels and intestinal permeability are elevated prior to arthritis onset, with this barrier dysfunction being microbiota-driven. Transfer of CIA-derived gut microbiota to germ-free (GF) recipients results in increased gut permeability. Moreover, pre-arthritic administration of a zonulin antagonist selectively restores epithelial integrity and reduces subsequent joint inflammation (39). Hypoxia-inducible factor (HIF) plays a pivotal role in regulating tight junction proteins such as claudin-1, thereby orchestrating adaptive barrier responses in the mucosa (44,45). HIF-2α, specifically expressed in the mucosal epithelium, is essential for maintaining gut barrier integrity and regulating intestinal iron absorption. Certain bacterial metabolites, such as 1,3-diaminopropane, reuterin, and short-chain fatty acids (SCFAs), suppress HIF-2α, influencing intestinal barrier function (46). Wen *et al* (42) demonstrated that inhibiting intestinal HIF-2α preserves epithelial barrier integrity by selectively downregulating claudin-15, thereby reducing arthritis severity. Consequently, restoring intestinal tight junctions may be a key intervention in the prevention and treatment of RA.

Dysregulation of mucosal immune response. Studies suggest that the initiation of autoimmune responses in RA begins in gut-associated lymphoid tissue (GALT), distant from the joints, involving both innate and adaptive immune responses (5,39,47,48). Increased intestinal permeability facilitates the transport of intestinal immune cells to the joints. Takahashi *et al* (49) performed cell transport analysis using KikGR mice and observed that both follicular helper T (Tfh) cells and B cells migrated from the colonic patch to the draining lymph nodes following immunization. In the CIA model, it has been confirmed the distal GALT is a primary site for initiating the autoimmune response. The intestinal lamina propria is recognized as the main source of T helper 17 (Th17) cells, and during the immune initiation phase in CIA mice, an increase in Th17 cell content in intestinal lamina propria correlates strongly with arthritis severity (47,50,51). In transgenic K/BxN arthritis mice, a population of α4β7-expressing Th17 cells was found in the spleen, where they assist in the generation of autoantibodies against glucose-6-phosphate isomerase (52). Another potential source of $\alpha4\beta7^{+}$ Th17 cells in the spleen is the migration of intestinal $CD103^{+}$ dendritic cells (DCs) to the spleen. Marietta *et al* (38) demonstrated that $CD103^{+}$ DCs, located in the intestinal lamina propria, migrate to the spleen in CIA mice, suggesting that these DCs may have originated from the intestine.

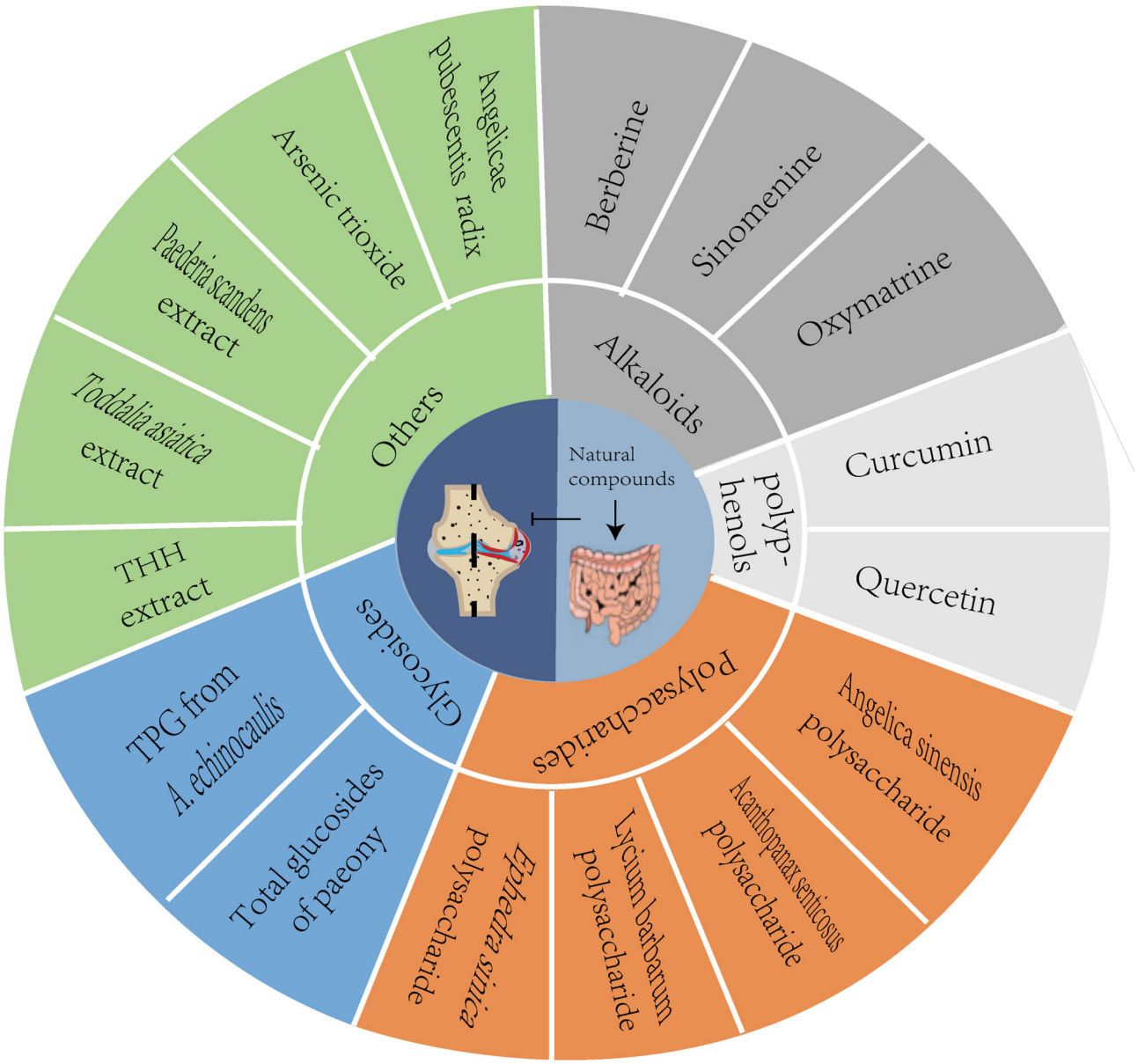

Figure 2. Natural compounds for the treatment of RA based on the 'gut-joint axis'. RA, rheumatoid arthritis; TPG, total polysaccharide and glycoside; THH, *Tripterygium hypoglaucum* (Levl.) Hutch.

Molecular mimicry. Molecular mimicry, a process in which microbial antigens share structural similarities with autoantigens, can lead to the cross-activation of autoreactive T or B cells, thereby triggering autoimmunity. Certain gut microbiota have been implicated in causing autoimmune responses and systemic inflammation through molecular mimicry, resulting in joint tissue damage (53). For instance, *Escherichia coli* heat-shock protein (DnaJ) shares a molecular mimicry mechanism with the *HLA-DRB1*0401* molecule, as both exhibit the amino acid sequence QKRAA (54). Preclinical RA studies have identified potential epitopes in *Citrobacter*, *Clostridium*, *Bacteroides* and *Eggerthella* that resemble collagen XI and *HLA-DRB1*0401* epitopes (12,13,55,56). Additionally, *Bacteroides fragilis 3_1_12*, a strain from the *Bacteroidaceae* family, may mimic the collagen II peptide (57-59). Similarly, *Prevotella* epitopes show high sequence homology with T-cell epitopes of N-acetylglucosamine-6-sulfonamide and serpin A, presented by *HLA-DR* (60-62). These microorganisms may trigger autoimmune responses and antibody production *via* molecular mimicry, thereby accelerating RA progression. Thus, molecular mimicry may represent a key mechanism by which the gut microbiota influences the pathogenesis and development of RA.

Disruption of microbial-derived metabolites. The disruption of metabolites derived from the intestinal microbiota plays a pivotal role in the 'gut-joint axis' of RA. Preclinical high-risk populations have already shown intestinal microbiota dysbiosis and alterations in metabolomics (5). Among these metabolites, SCFAs have been studied most extensively studied and are considered key immunomodulatory compounds closely associated with RA (63). SCFAs primarily exert their effects on the immune system by modulating histone acetyltransferases and deacetylases (64). In patients with RA, fecal levels

of acetate, propionate, butyrate, and valerate are markedly reduced (49,63,65), with a characteristic deficiency of butyrate producers and an enrichment of butyrate consumers in the intestinal microbiota of these individuals (66,67). The protective role of butyrate in RA has been widely investigated, particularly its effects on balancing Th17 and T regulatory (Treg) cells in the intestine system, as well as its regulation of B cells and autoantibody production (63,67,68). Additionally, Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis has revealed alterations in amino acid and lipid metabolism in PreRA and established patients with RA (5,69). A retrospective clinical cohort study in Sweden found that patients with RA and positive ACPA exhibited elevated levels of lysophospholipid and tryptophan metabolism several years before diagnosis, compared with undiagnosed individuals with RA (70). Following this, Seymour *et al* (71) demonstrated in animal studies that indole, a tryptophan metabolite produced by bacteria such as *P. copri*, *Collinsella* and *Ruminococcu*s, plays a pivotal role in the development of CIA by enhancing Th17 immunity both locally in the gut and systemically. Bile acids (BAs) are vital for immune regulation, particularly in balancing Th17 and Treg cell populations (72-75), and contribute to the maintenance of fat metabolism. However, high concentrations of BAs can have cytotoxic effects on colonic epithelial cells (76). While studies on BA levels in RA animal models remain inconclusive (77-79), accumulating evidence suggests that BAs play a protective and preventative role in RA (18,80).

Regulation of intestinal hormones. The intestine harbors a significant number of endocrine cells that secrete various intestinal hormones. Hormones such as vasoactive intestinal peptide (VIP), somatostatin (SOM), substance P (SP) and gastrin-releasing peptide are implicated in the progression of RA (81-83). VIP can promote the Th1/Th2 balance and enhance the differentiation of Treg cells and follicular regulatory T (Tfr) cells, thereby reducing joint inflammation in RA animal models (84-86). SP has been reported to stimulate the proliferation of synovial cells (87,88) and serum SP levels are considered indicative of disease activity and subclinical inflammation in patients with RA (89). However, other studies suggest that SP treatment can reduce inflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin-17 (IL-17), while increasing the expression of the anti-inflammatory cytokine IL-10, leading to significant improvements in RA symptoms (90,91). Consequently, the exact mechanism by which SP influences RA remains to be further elucidated.

Sex bias. Significant sex differences exist in RA, with a prevalence rate in females that is notably higher than in males, often at a ratio of 4:1 or more (92,93). The influence of sex hormones on RA has been extensively studied. A sudden drop in estrogen levels and a decrease in androgen can both increase RA risk (94). Sex hormone deficiency enhances intestinal permeability, expands the Th17 cell pool and upregulates osteoclastogenic factors, such as TNF-α, RANKL and IL-17, in the bone marrow, with the gut microbiota playing a central role in this process (95). However, butyrate supplementation has been shown to prevent estrogen-deficiency-induced bone loss (96) and alleviate arthritis by activating the estrogen-related receptor α on Th17 cells, modulating IL-17 and IL-10 production (68). Sex-specific differences in the gut microbiota have been well established (97). Compared to women, men have markedly lower levels of *Prevotella* (36) and *P. copri* antibodies, which are considered specific to RA, exhibit a sex disparity, with a male-to-female ratio of 1:9. This difference may markedly contribute to the female predominance observed in RA (28). Additionally, *Eggerthella lenta (E. lenta)*, a potential pathogenic bacterium in RA, is found in higher levels in female patients with RA (98). Animal studies have shown that female mice treated with *E. lenta* display increased intestinal permeability, elevated IgG-RF levels, an expansion of IL-17- and IFN-γ-producing B cells, and higher concentrations of BAs and succinyl carnitine, indicating a sex-specific immune response to *E. lenta* (98). Despite some evidence, the role of sex-dependent differences in the human microbiota in RA remains poorly understood. Preclinical and clinical data are both still limited, and more comprehensive evidence is needed to support or challenge these findings.

4. Natural compounds for the treatment of RA based on the 'gut-joint axis'

Natural compounds exert a positive effect on human health by regulating various mechanisms, offering potential therapeutic benefits for a range of diseases. Several natural compounds, including sinomenine and *Tripterygium wilfordii* are widely used in the clinical treatment of RA in China. Clinical studies exploring the use of natural compounds for RA treatment have entered the initial exploration stage (Table I). However, these studies face challenges such as low quality, weak evidence and small sample size, necessitating high-quality clinical trials to improved support the therapeutic effects of these compounds on RA. Basic research has consistently confirmed the protective effects of natural compounds on RA, elucidating the underlying mechanisms. For most high-molecular-weight, low-bioavailability natural compounds, which accumulate in large quantities in the gastrointestinal tract after oral administration, the intestine appears to be a key target for their action in treating RA. This section focuses on natural compounds that treat or enhance RA therapy through the 'gut-joint axis' (Table II).

Alkaloids. Alkaloids, primarily found in plants, are key components of numerous Chinese herbal medicines. Higher plants from the Liliaceae, Berberidaceae, Ranunculaceae, Leguminosae, Amaryllidaceae, Papaveraceae and Solanaceae families are rich in alkaloids. These compounds are characterized by nitrogen atoms in their chemical structure, which is a defining feature and their biological efficacy is attributed to the specific arrangement of atoms in their molecular structure (99). Alkaloids exhibit significant biological activities, including antibacterial, antiviral, anti-inflammatory, and anti-tumor effects, suggesting their potential medicinal value in the RA treatment (100-102).

Berberine. Berberine, an isoquinoline alkaloid extracted from various medicinal plants such as Coptis, Phellodendron and Berberis, possesses a broad range of pharmacological effects, including anti-tumor, anti-oxidative, anti-inflammatory, hypoglycemic and lipid-lowering properties. Clinical

Table I. Clinical research on the treatment of RA with natural compounds.

First author/s, year	Natural compound	Country	Therapeutic drugs and dosage	Route of administration and treatment duration	Key findings	(Refs.)
Liu *et al*, 2018	Sinomenine	China	Experimentalgroup (n=25): Sinomenine 60-120 mg, twice a day. Control group (n=24): MTX 7.5-10 mg, once a week.	Oral administration, 24 weeks	1. There was no significant difference in controlling the secretion of these cytokines (IL-6, IL-12, IL-1α, IL-1β and TNF-α) between sinomenine and MTX. 2. Sinomenine and MTX both significantly improved the patients' DAS28 scores, with no statistically significant difference observed between the two treatments.	(114)
Huan *et al*, 2019		China	Experimental group (n=73): Sinomenine 120 mg, twice a day; MTX 10 mg, once a week. Control group (n=47): LEF 20 mg, once a day; MTX10 mg, once a week.	Oral administration, 24 weeks.	1. There was no significant difference between MTX combined with sinomenine and MTX combined with LEF in improving the disease activity index or reducing the disease activity rate. 2. Compared with MTX plus LEF, MTX combined with sinomenine resulted in a significantly lower incidence of gastrointestinal adverse events and hepatotoxicity.	(115)
Chen *et al*, 2025		China	Experimental group (n=50): Sinomenine 60 mg, 3 times a day; MTX 10 mg, once a week. Control group (n=51): MTX 10 mg, once a week.	Oral administration, 12 weeks	1. There was no significant difference in American college of rheumatology 20% improvement criteria response between the two groups of patients. 2. Compared with the patients in the control group, the C-reactive protein of the patients in the experimental group was significantly lower, and the patients' sensory indicators were significantly improved.	(116)

Table I. Continued.

First author/s, year	Natural compound	Country	Therapeutic drugs and dosage	Route of administration and treatment duration	Key findings	(Refs.)
Shi *et al*, 2018	Oxymatrine	China	Experimental group (n=68): oxymatrine 25 mg, twice a day; indomethacin 25 mg, 3 times a day; MTX 10 mg, once a week. Control group (n=68): Indomethacin 25 mg, 3 times a day; MTX 10 mg, once a week.	Oral administration, 24 weeks.	1. In the experimental group supplemented with oxymatrine, improvements in CRP, erythrocyte sedimentation rate and DAS28 scores were significantly improved compared with those in the control group. 2. After treatment, the experimental group exhibited a pronounced increase in peripheral blood Treg cells and a marked decrease in Th17 cells compared with pretreatment levels, whereas no significant changes in Treg or Th17 cells were observed in the control group.	(132)
Li *et al*, 2019		China	Experimental group (n=68): oxymatrine 25 mg, twice a day; Indomethacin 25 mg, 3 times a day. Control group (n=68): Indomethacin 25 mg, 3 times a day.	Oral administration, 24 weeks.	Compared with the control group, the experimental group showed a more pronounced reduction in morning stiffness duration and joint tenderness, along with significantly greater decreases in the inflammatory markers IL-6, TNF-α and CRP.	(133)
Chandran *et al*, 2012	Curcumin	India	Group I (n=14): Curcumin 500 mg, twice a day. Group II (n=12): Curcumin 500 mg, twice times a day; diclofenac sodium 50 mg, once a day. Group III (n=12): Diclofenac sodium 50 mg, once a day.	Oral administration; 8 weeks.	1. After treatment, DAS28 scores significantly decreased in all three groups, with the Group I showing the most pronounced improvement. 2. In terms of adverse-event incidence, curcumin monotherapy demonstrated the highest safety profile.	(137)

Table I. Continued.

First author/s, year	Natural compound	Country	Therapeutic drugs and dosage	Route of administration and treatment duration	Key findings	(Refs.)
Pourhabibi-Zarandi *et al*, 2024; Pourhabibi-Zarandi *et al*, 2022		Iran	Experimental group (n=24, female): Curcumin 500 mg, once a day, current medication, Control group (n=24, female): Placebo capsules 500 mg, once a day; current medication.	Oral administration; 8 weeks.	1. Compared with the control group, the experimental group showed significant improvements in pain, swelling, and DAS28 scores. 2. Compared with the control group, patients in the experimental group exhibited a significant increase in serum TAC and marked reductions in CRP and ESR levels. 3. Compared with the control group, patients in the experimental group showed significant improvements in metabolic parameters such as triglycerides and body weight.	(138,139)
Amalraj *et al*, 2017		India	Group I (n=12): Curcumin 250 mg, twice a day. Group II (n=12): Curcumin 500 mg, twice a day. Group III (n=12): Placebo capsules 500 mg, once a day.	Oral administration; 12 weeks.	1. Patients receiving both low- and high-dose curcumin showed significant improvements in DAS28 scores, ACR responses, ESR, CRP and rheumatoid factor levels compared with group III, with the high-dose group exhibiting the most pronounced therapeutic effects. 2. No side effects or adverse reactions were observed in either curcumin-treated group.	(140)
	/	Canada	Experimental group:Curcumin 180 mg/day; vitamin D: 2,000 IU, once a day; Omega-3 900 mg, once a day.	Oral administration; 12 weeks.	1. The primary objective of this study will determine if the level of ACPA is altered after taking curcumin, omega-3, and vitamin D for 3 months. 2. The secondary objective is to determine the safety and tolerability of vitamin D in the study population. 3. Exploratory outcomes will include assessment of joint, symptoms, blood biochemistry and hematology.	NCT06478290

Table I. Continued.

First author/s, year	Natural compound	Country	Therapeutic drugs and dosage	Route of administration and treatment duration	Key findings	(Refs.)
Javadi *et al*, 2017	Quercetin	Iran	Experimental group (n=25, female): Quercetin 500 mg, once a day; current medication. Control group (n=25, female): Placebo capsules 500 mg, once a day, current medication	Oral administration; 8 weeks.	1. Compared with the control group, quercetin significantly reduced morning stiffness, pain, DAS28 scores and plasma TNF-α levels. 2. Quercetin did not exert a significant effect on joint swelling or ESR.	(146)
Javadi *et al*, 2014		Iran	Experimental group (n=20): Quercetin 500 mg, once a day; current medication. Control group (n=20): Placebo capsules, 500 mg, once a day; current medication.	Oral administration; 8 weeks.	Compared with the control group, quercetin had no significant effects on patients' plasma TAC, inflammatory status (e.g., CRP), or blood pressure.	(147)
Chen *et al*, 2013	Total glucosides of paeony	China	Experimental group (n=105): TGP 0.6 g, 3 times a day; MTX 10 mg, once a week; LEF 20 mg, once a day. Control group (n=89): MTX 10 mg, once a week; LEF 20 mg, once a day.	Oral administration; 24 weeks.	1. Significantly less frequent hepatotoxicity was observed in patients with TGP than those without at 12 weeks. 2. Although the differences were not statistically significant, a greater proportion of patients in the experimental group achieved EULAR good or moderate responses at weeks 12 and 24.	(175)
Xiang *et al*, 2015		China	Experimental group (n=132): TGP, 0.6 g, 3 times a day, MTX 10-15 mg, once a week; LEF 20 mg, once a day. Control group (n=136): MTX 10-15 mg, once a week, LEF 20 mg, once a day.	Oral administration; 12 weeks.	1. At week 12, the incidence of hepatic dysfunction in the experimental group was significantly lower than in the control group. 2. Although the difference did not reach statistical significance, more patients achieved remission, good and moderate response in experimental group than control group. 3. The incidence of diarrhea was higher in the experimental group than in the control group; no significant differences were observed for any other adverse events between the two groups.	(176)

Table I. Continued.

First author/s, year	Natural compound	Country	Therapeutic drugs and dosage	Route of administration and treatment duration	Key findings	(Refs.)
Wang *et al*, 2007	Tripterygium	China	Experimental group (n=180): TGP 0.2 g, 3 times a day; MTX 10 mg, once a week. Control group (n=80): Sulfasalazine 1.0 g, twice a day; MTX 10 mg, once a week.	Oral administration; 12 weeks.	Compared with the control group, patients in the experimental group showed significantly greater improvements in morning stiffness duration, joint swelling, and inflammatory markers such as ESR and CRP.	(177)
		China	Experimental group (n=150): *Tripterygium wilfordii* Hook F 20 mg, 3 times a day; MTX 10 mg, once a week. Control group (n=150): MTX 10 mg, once a week.	Oral administration; 24 weeks.	The primary outcome is the percentage of participants with American College of Rheumatology 20% at week 24.	NCT04136262
/		China	Experimental group (n=150): *Tripterygium wilfordii* Hook F 20 mg, 3 times a day; placebo 10-15 mg, once a week. Control group (n=150): MTX 10-15 mg, once a week; placebo 20 mg, 3 times a day.	Oral administration; 24 weeks.	1. The primary endpoint is the change from baseline in DAS28 at week 24. 2. Secondary endpoints are the proportion of patients achieving ACR20/50/70, the change from baseline in the HAQ score and van der Heijde Sharp score, as well as the number of adverse events.	NCT03337815

RA, rheumatoid arthritis; MTX, methotrexate; LEF, leflunomide; IL-6, interleukin 6; TNF-α, tumor necrosis factor α; DAS28, disease activity score based on 28 joints; CRP, c reactive protein; TAC, total antioxidant capacity; ACR, American College of Rheumatology; ESR, erythrocyte sedimentation rate; ACPA, anti-citrullinated protein antibody; TGP, total glucosides of paeony; EULAR, European league against rheumatism; HAQ, health assessment questionnaire.

Table II. Natural compounds for the treatment of RA based on the gut-joint axis.

First author/s, year	Category	Natural compound	Subjects	Changes in gut microbiota after treatment	Additional 'intestinal joint axis' mechanisms	(Refs.)
Yue *et al*, 2017	Alkaloids	Berberine	CIA Wistar rats	/	Berberine exerts its anti-arthritis effect by enhancing the autocrine/paracrine secretion of intestinal nerve cells and endocrine cells to induce the production of corticostatin in the intestine, thereby inhibiting the Th17 cell response.	(110)
Yue *et al*, 2019			CIA Wistar rats	1. Diversity and richness of the gut bacteria↓ 2. The abundance of butyrate-producing bacteria↑ and *Prevotella*↓	Berberine induces the production of butyrate by promoting the expression of BUT, thus countering RA.	(112)
Tong *et al*, 2015		Sinomenine	CIA Wistar rats	/	Sinomenine regulates the balance between intestinal Th17/Treg cells and the migration of Th17 and Treg cells in the intestine and joints.	(120)
Yue *et al*, 2018			CIA Wistar rats	/	Intestine-sourced VIP mediates the anti-arthritic effect of sinomenine.	(124)
Gao *et al*, 2023		Oxymatrine	CIA DBA/1J mice	Family: *Firmicutes*↓; *Bacteroidota*, *Patescibacteria* and *Campylobacterota*↑ Genus: g_*Ligilactobacillus*↓	Transcriptomic analysis showed that Oxymatrine regulates the proportion of Th cells in the gut and balances the immune system.	(131)
Yang *et al*, 2015	Polyphenols	Curcumin	AIA SD rats	/	Curcumin inhibits the progression of arthritis by increasing intestinal hormone SOM.	(145)
Piovezana *et al*, 2019		Quercetin	AIA Holtzman rats	/	Quercetin can improve the damage to the enteric nervous system and mucosa caused by RA while treating RA.	(152)
Silva *et al*,2024			AIA Holtzman rats	/	The combination of quercetin and ibuprofen exhibits favorable enteric neuroprotective effects.	(153)
Hu *et al*, 2022	Polysaccharides	*Angelica sinensis* polysaccharide	CIA Wistar rats	Family: *Oscillospiraceae*↓ Genus: *Lactobacillus*, *norank_o_clostridia_ucg-014*, *UCG-005*, *norank_f_oscillospiraceae* and *Candidatus_Saccharimonas*↑; *norank_f__Oscillospiraceae*, *norank_f__Desulfovibrionaceae*, *norank_f__Ruminococcaceae*, *Roseburia*↓	*Angelica sinensis* polysaccharide can upregulate the expression of the Claudin-5 gene, thereby improving the tight junctions of intestinal epithelial cells in CIA rats.	(27)

Table II. Continued.

First author/s, year	Category	Natural compound	Subjects	Changes in gut microbiota after treatment	Additional 'intestinal joint axis' mechanisms	(Refs.)
Luo *et al*, 2025			CIA Wistar rats	1. Diversity and richness of the gut bacteria↑ 2. Genera: *Candidatu_ Saccharimonas*, *Lactobacillus*, *Bifidobacterium*, *Faecalibaculum*, *noran_f_Ruminococcaceae*, *Parvlbacter*, *Fournierella*, *Alloprevotella*↑	Metabolites of gut bacteria, such as myristoleic acid, cuminaldehyde, 4-deoxypyridoxine and galactosylhydroxylysine, are key to the alleviation of RA by *Angelica sinensis* polysaccharide.	(156)
Liu *et al*, 2023	Polysaccharide	*Acanthopanax senticosus* polysaccharide	CIA DBA/1J mice	1. The α diversity of intestinal microbiota↑ 2. Phylum: *Bacteroides*↓; *Bacteroidetes/Firmicutes*↓ Genus: *Ruminococcus*, *GCA-900066575*, *Colidextribacter*, *Blautia* and *Acetatifactor*↑	GGC may act as a metabolite of the gut microbiota responsible for the anti-CIA effect of *Acanthopanax senticosus* polysaccharide.	(162)
Lai *et al*, 2022		*Lycium barbarum* polysaccharide	CIA Wistar rats	Genera: *Romboutsia, Lactobacillus*, *Dubosiella and Faecalibaculum*↑ *Lachnospiraceae_ NK4A136_ group* and *uncultured_bacterum_f_ ruminococcaceae*↓	1. *Lycium barbarum* polysaccharide increases the abundance of gut microbiota that produce S-adenosyl methionine and inhibits the expression of RA-related genes in intestinal epithelial cells, thereby suppressing the activity of CIA 2. The downregulation of RA-related gene expression in intestinal epithelial cells is associated with the increased levels of S-adenosyl methionine.	(170)
Liu *et al*, 2023			CIA Wistar rats	Genera: *Romboutsia, Lactobacillus*, *Turicibacter, Clostridium*_sensen_stricto_1, *Faecalibacterium* and *Adlercreutzia*↑	The fermentation metabolites of bacteria on LBP, rather than LBP itself, may be the reason for the improvement of RA.	(171)
Ma *et al*, 2024		Ephedra sinica polysaccharide	CIA C57BL/6J mice	Genera: *Dubosiella*, *Roseburia*, *Bifidobacterium*, *Clostridium*, *Pseudoramibacter*, *Faecalibaculum* and *Parabacteroides*↑; *Alistipes*, *Enterococcus*, *Enterorhabdus*, *Odoribacter* and *Escherichia*↓	*Ephedra sinica* polysaccharide improves intestinal microbial metabolism and mucosal barrier while treating CIA.	(174)

Table II. Continued.

First author/s, year	Category	Natural compound	Subjects	Changes in gut microbiota after treatment	Additional 'intestinal joint axis' mechanisms	(Refs.)
Peng *et al*, 2019	Glycosides	Total glucosides of paeon	CIA SD rats	Phylum: *Tenericutes*↑ Class: *Mollicutes*↑ Order: *Mollicutes RF9*↑ Family: *Christensenellaceae*↑ Genera: *Christensenellaceae R-7*, *Anaerovorax* and *unclassified_erysipelotricaceae*, *Anaerovorax*↑	Total glucosides of Paeon inhibit the levels of intestinal cytokines and secretory immunoglobulin A and regulate the intestinal mucosal immune response.	(184)
Li *et al*, 2021		Total polysaccharide and glycoside from *A. echinocaulis*	CIA SD rats	Phylum: *Acidobacteria*, *Gemmatimonadetes*, *Proteobacteria*, *Gemmatimonadees*↑ *Kiritimatiellaeota*, *atescibacteria*, *Tenericutes*, *Fusobacteria* and *Kiritimatiellaeota*↓ Genera: *Ruminantiom_group*, *Helicobacter*, *Parasutterella*, *Prevotella_1*, *Prevotella_9*, *Rikenellaceae_RC9_gut_group*↑ *Ruminococcaceae_UCG-014, Ruminococcus_1*↓	KEGG pathway and COG functional analyses suggest that the total polysaccharides and glycosides from *A. echinocaulis* may combat RA by modulating the gut microbiota, which in turn regulates the production of metabolites.	(186)
Hu *et al*, 2023	Others	*Tripterygium hypoglaucum* (Levl.) Hutch	AIA C57BL/6 mice	Families: *Bifidobacteriaceae*, *Verrucomicrobiaceae*, *Oxalobacteraceae* and *Erysipelotrichaceae*↑ *Genus: Bifidobacterium*, *Lactobacillus*, *Akkermansia*, *Turicibacter*, *Faecalibaculum* and *Ruminiclostridium*↑ *Butyricimonas*, *Parabacteroides*, *Bacteroides*, *Desulfovibrio*, *Anaeroplasma*, *Marvinbryantia*↓	The anti-AIA effect of *Tripterygium hypoglaucum* (Levl.) Hutchcan is dependent on the gut microbiota and it can elevate the content of short-chain fatty acids in AIA mice and participate in the metabolic pathways of the gut microbiota.	(190)

Table II. Continued.

First author/s, year	Category	Natural compound	Subjects	Changes in gut microbiota after treatment	Additional 'intestinal joint axis' mechanisms	(Refs.)
Zheng *et al*, 2023			AIA C57BL/6 mice	/	1. The anti-inflammatory effect of *Tripterygium hypoglaucum* (Levl.) Hutch on AIA in mice is dependent on the gut microbiota, and it can inhibit the expression of pro-inflammatory cytokines in the gut. 2. Bile acids play a pivotal role in the anti-arthritic efficacy of *Tripterygium hypoglaucum* (Levl.) Hutch.	(191)
Qin *et al*, 2023		*Toddalia asiatica* extract	AIA SD rats	1. The α diversity of intestinal microbiota↑ 2. Phylum: *Desulfobacterota*↑ Genera: *Lactobacillus*, *Firmicutes_unclassified*, *Ruminococcaceae_unclassified*, *Muribaculum*, *Subdoligranulum*, *Lachnospira*, *Marvinbryantia*↑; *Ligilactobacillus*, *Streptococcus*, *Eubacterium-eligens-group*↓	*Toddalia asiatica* extract can modulate the imbalance of Th17/Treg cells in the gut and ameliorate the intestinal inflammation that occurs during the development of AIA, while also regulating the metabolic pathways of the gut microbiota.	(197)
Xiao *et al*, 2018		*Paederia scandens* extract	CIA DBA/1 mice	Genera: *S24-7* and *Rikenella*↑; *Mucispirillum*, *Rikenellaceae_RC9*, *Desulfovibrio*, *Helicobacter* and *Lachnospiraceae*↓	/	(199)
Niu *et al*, 2022		Arsenic trioxide	CIA DBA/1J mice	1. Diversity and richness of the gut bacteria↑ 2. Phylum: *Bacteroidetes*↑; *Lactobacillales*, *Firmicutes*↓ Genera: *Alistipes*↑; *HT002*↓	Arsenic trioxide can partially reverse the abnormal fecal metabolites in CIA mice.	(204)
Chen *et al*, 2023		Columbianadin	CIA DBA/1J mice	Family: *Lachnospiraceae*, *Rikenellaceae* and *Lactobacillus*↑; *Muribaculaceae*, *Ruminococcaceae* and *Intestinimonas*↓	Columbianadin can regulate the metabolic disorders in serum and urine of CIA mice.	(209)

RA, rheumatoid arthritis; CIA, collagen-induced arthritis; BUT, butyryl-CoA: acetate CoA transferase; VIP, vasoactive intestinal peptide; AIA, adjuvant-induced arthritis; SOM, somatostatin; GGC, γ-glutamylcysteine; LBP, *Lycium barbarum* polysaccharide; KEGG, Kyoto Encyclopedia of Genes and Genomes; COG, Clusters of Orthologous Groups of proteins.

studies have reported its therapeutic efficacy in treating conditions such as cancer, digestive system disorders, and metabolic diseases (103-107). Due to its ability to inhibit toxins and bacteria and protect the intestinal mucosal barrier, berberine has shown significant advantages in the treatment of digestive disorders (108). A large portion of orally administered berberine remains in the intestine, with an extremely low bioavailability of only 0.1% (109). Oral administration of 200 mg/kg berberine markedly improved CIA in rats, although the peak drug concentration in the blood was <0.06 μM (110), which is much lower than the *in vitro* minimum effective concentration of 1-50 μM (109,111). Additionally, intravenous berberine did not improve arthritis in rats, suggesting that its anti-arthritis effects are intestinally dependent (110). Further mechanistic studies revealed that oral berberine selectively increased cortistatin levels, a neuropeptide derived from the intestine, both in the intestines and serum of arthritic rats. It also promoted cortistatin expression in intestinal nerve and endocrine cells. The upregulated cortistatin then entered systemic circulation, where it suppressed the immune response of Th17 cells, alleviating arthritis symptoms (110). Moreover, berberine markedly increased the levels of intestinal SCFAs, particularly butyrate, enhanced the abundance of butyrate-producing bacteria and stimulated the expression and activity of butyryl-CoA: Acetate CoA transferase (BUT) (112). When BUT inhibitors or broad-spectrum antibiotics were applied, the regulatory effect of berberine on the intestinal internal environment and its anti-arthritis effects were markedly reduced, indicating that berberine promotes butyrate production through the intestinal microbiota, positioning it as a potential therapeutic agent for RA (112). This effect is highly dependent on the intestinal microbiota (112).

Sinomenine. Sinomenine is an alkaloid extracted from the roots and stems of *Sinomenium acutum* and has demonstrated immunosuppressive and anti-arthritis effects (113). In China, sinomenine is widely used in clinical RA treatment and has been shown to improve arthritis symptoms and reduce inflammatory markers in patients (114-116). A study utilizing multicriteria decision analysis to evaluate the benefits and risks of sinomenine preparations in RA treatment found that combining sinomenine with conventional drugs yielded greater benefits than using it alone (117). However, animal studies have shown that oral administration of sinomenine does not achieve the minimum effective concentration in the synovium or serum (≥250 μM) required for *in vitro* efficacy, indicating that its precise anti-arthritis mechanism remains to be fully elucidated (118-120). Sinomenine may exert anti-inflammatory effects by inhibiting macrophage activation *via* the α 7-nicotinic acetylcholine receptor (α7nAChR) (121-123). Subsequent studies exploring the anti-arthritis mechanism of sinomenine through the neuro-endocrine-inflammation axis revealed that oral sinomenine treatment improved systemic inflammation in CIA rats. It was found to interact with the residues Tyr184 and Tyr191, binding to α7nAChR and activating the α7nAChR-PI3K/Akt/mTOR pathway, which selectively promotes the generation of VIP in intestinal neuron-like cells of CIA rats (124). Research by Tong *et al* (120) further confirmed that the protective effect of sinomenine in CIA is intestine-dependent. Oral administration of sinomenine reduced the arthritis score in CIA rats, decreased serum IL-17A levels and increased IL-10 levels. Additionally, sinomenine increased the frequency of Treg cells in intestinal lymphoid tissue, decreased Th17 cell frequency and markedly elevated α4β7-positive cells in the joints. These findings suggest that sinomenine regulates immune cell migration within the gut-joint axis, facilitating lymphocyte migration from the intestine to the joint, thereby alleviating RA symptom. Notably, when administered intraperitoneally, sinomenine loses its therapeutic effect on arthritis.

Oxymatrine. Matrine, a natural bioactive compound extracted from the roots of the leguminous plant *Sophora flavescens*, is one of its main pharmacologically active components. It possesses a broad range of pharmacological and biological effects, including antiviral, anti-tumor, antioxidant and antibacterial properties, with the added advantage of low toxicity and minimal side effects (125). A number of studies have demonstrated that matrine can effectively alleviate arthritis symptoms in RA model animal by regulating immune responses, inhibiting synovial vessel formation, and suppressing fibroblast-such as synovial cell proliferation, among other mechanisms (126-128). Oxymatrine, a derivative of matrine with a distinct oxygen structure, exhibits similar pharmacological effects. Animal studies have shown that oxymatrine also exerts anti-RA effects (129-131). In CIA mice, oxymatrine treatment markedly improved arthritis symptoms, reduced the abundance of *Firmicutes* in the gut and increased the abundance of *Bacteroidota*, *Patescibacteria* and *Campylobacterota*, thereby reshaping the gut microbiota towards more normal levels (131). Moreover, oxymatrine treatment corrected the imbalance in $CD4^+$ T cell subsets in CIA mice, restoring intestinal immune balance by regulating the Th1/Th2, Treg/Th17 and Tfr/Tfh cell ratios (131). Limited clinical studies also suggest that adding oxymatrine to routine RA treatment can more effectively reduce inflammatory markers and balance the immune response in patients (132,133).

Polyphenols. Polyphenols, commonly found in plants such as vegetables, fruits and soybeans, consist primarily of aromatic rings and hydroxyl groups. These compounds are renowned for their potent anti-inflammatory and antioxidant properties, which offer significant benefits for human health and the prevention of chronic diseases. Due to these properties, polyphenols are emerging as promising candidate drugs for the management of RA.

Curcumin. Curcumin, the main active compound in turmeric, directly targets the intestines and exhibits potent anti-inflammatory, immune-regulatory and intestinal microbiota-modulating effects (134,135). Extensive basic and clinical studies have confirmed curcumin's significant benefits in improving RA (136). In clinical settings, curcumin not only alleviates symptoms and reduces serum inflammatory markers but also demonstrates a high safety profile (137-140). However, curcumin is characterized by poor gastrointestinal absorption and low oral bioavailability, with an absolute bioavailability of only 1%. In rats, oral administration of 100 mg/kg curcumin resulted in a plasma peak of only 0.02 μM, far below the minimum effective concentration of 10 μM needed to inhibit synovial cell and lymphocyte activation *in vitro* (141-144). Consequently, curcumin's therapeutic effects on RA may be primarily mediated through its extensive pharmacological

effect on the intestine. Yang *et al* (145) indicated that the anti-arthritis effects of oral curcumin depend on the intestine. Curcumin activates the cAMP/PKA and $Ca2^{+}$/CaMKII signaling pathways, increasing the number of SOM-positive cells in the small intestine and raising SOM levels in both the intestine and serum. This process alleviates inflammation and immune dysfunction, thereby inhibiting the progression of adjuvant-induced arthritis (AIA) in rats. However, when a SOM inhibitor is used or curcumin is administered intraperitoneally, this anti-arthritis effect is markedly diminished.

Quercetin. Quercetin, a flavonoid commonly found in fruits and vegetables, possesses multiple biological activities, including anti-inflammatory, antioxidant, anti-cancer and liver-protective effects. Clinical studies on quercetin for treating RA are limited. While quercetin appears to positively affect arthritis symptoms, its ability to enhance antioxidant capacity and modulate inflammation in patients with RA remains controversial (146,147). Animal studies, however, have shown that quercetin's potent antioxidant properties not only improve RA but also alleviate side effects caused by traditional RA treatments (148,149). Moreover, research has demonstrated that RA is associated with enteric neurodegenerative changes that impair intestinal functions such as absorption, secretion, and immunity (150,151). Oral administration of quercetin can increase the expression of glial cell-derived neurotrophic factor, glial fibrillary acidic protein and VIP in the intestine. This effect helps reverse the decreased density of intestinal neurons and glial cells in RA mice, restores the morphological changes in the myenteric and submucosal plexuses, and alleviates both intestinal and joint inflammation (152,153).

Polysaccharides. Natural polysaccharides are macromolecular substances primarily extracted from plants, algae, animals, fungi and bacteria. These polysaccharides exhibit a wide range of important biological activities, including anti-hyperlipidemic, antioxidant, anti-tumor, anti-hepatotoxicity, and immunomodulatory effects (154). Several Chinese herbal medicines, such as *Angelica sinensis*, wolfberry, *Acanthopanax senticosus* and *Ephedra*, contain natural polysaccharides that have been shown to alleviate RA by protecting the intestines and modulating the intestinal microbiota.

Angelica sinensis polysaccharides (ASP). ASP, the main active components of *Angelica sinensis*, enhance immunity and are non-starch polysaccharides that are not digested by the small intestine but serve as a primary energy source for the intestinal flora in the large intestine, thus supporting intestinal health (155). ASP intervention has been shown to relieve joint swelling and inflammation in RA animal models. Pseudo-aseptic tests confirmed that this relief is dependent on specific intestinal bacteria, such as *Lactobacillus*, *Bifidobacterium* and *Faecalibaculum*. Moreover, the metabolites produced by these bacteria, resulting from the interaction between ASP and the microbiota, contribute to the improvement of RA (156). ASP also alters gene expression in the colon and the intestinal microbiota. It promotes the expression of *Cldn5* (a gene related to tight junctions), thereby enhancing the intestinal epithelial cell tight junctions in CIA mice, increasing the abundance of anti-inflammatory bacteria such as *Norank f Norank o Clostridia UCG-014*, *Lactobacillus*, *Norank f Oscillospiraceae* and *Norank f Desulfovibrionaceae* and reducing the migration of inflammatory factors. Additionally, ASP boosts the expression of proteins that inhibit osteoclast differentiation, such as Slit3 and Rgs18, promoting bone formation, and alleviating RA symptoms (27).

Acanthopanax senticosus polysaccharide (ASPS). In traditional Chinese medicine, *Acanthopanax senticosus* has long been used to treat arthritis (157,158). ASPS, one of its key active ingredients, possesses functions including immune regulation, antioxidation and anti-diabetic properties (159-161). Studies have explored the mechanism of ASPS in treating RA, indicating that its therapeutic effect in CIA mice is partly dependent on the gut microbiota. This is because when CIA mice were treated with an antibiotic cocktail, arthritis worsens and when both ASPS and an antibiotic cocktail were administered, the protective effect of ASPS on joints was markedly weakened (162). Non-targeted UPLCMS metabolomics analysis of serum samples and PICRUSt2 (a method for accurately predicting 16S rRNA functional genes) analysis of fecal samples revealed that, following ASPS treatment, γ-glutamylcysteine may act as a metabolite of the gut microbiota and contribute to the anti-CIA effect of ASPS. This effect is likely mediated through the inhibition of NLRP3 inflammasome activation by γ-glutamylcysteine, leading to a reduction in IL-1β and caspase-1 expression, thereby exerting an anti-inflammatory effect (162).

Lycium barbarum polysaccharide (LBP). LBP, a key active component of wolfberry, is not directly digested or absorbed by the human body. Instead, it reaches the large intestine where it is metabolized by the gut microbiota. LBP is highly valued for its medicinal properties, including enhancing barrier function, anti-inflammatory, antioxidant, anti-tumor effects and its ability to regulate the intestinal microbiota (163-167). LBP exerts an anti-CIA effect regulates chondrocyte proliferation, reduces the expression of inflammatory cytokines such as IL-1α, IL-1β, IL-12 and IL-17 and restores anti-inflammatory cytokine IL-10 levels (168-170). Additionally, LBP may alter the gut microbiota composition, increasing the abundance of microbial taxa that produce S-adenosylmethionine, which induces DNA hypermethylation of RA-related genes (such as *Dpep3*, *Gstm6*, *Slc27a2*, *Col11a2*, *Sycp2*, *SNORA22*) in intestinal epithelial cells. This suppresses gene expression, reduces inflammatory cytokine levels, and mitigates inflammation (170). The elimination of LBP's anti-CIA effect by antibiotics further suggests that its therapeutic action relies on the intestinal microbiota (171).

Ephedra sinica polysaccharide (ESP). *Ephedra*, a herbaceous plant, has a long history in Chinese medicine for treating colds, edema and other ailments. Studies have identified its anti-inflammatory properties, with its primary component, ESP, showing efficacy in improving RA symptoms (172,173). ESP modulates the intestinal microbiota and its metabolites. After ESP treatment, the gut microbiota dysbiosis in CIA mice was corrected, leading to increased abundances of *Dubosiella*, *Bifidobacterium*, *Clostridium* and *Pseudoramibactere*, elevated colonic butyrate levels, reduced ileal and colonic permeability, and alleviated intestinal inflammation (174). Additionally, the upregulation of HDAC1 and HDAC2 in response to intestinal inflammation induces NF-κB phosphorylation and activates TLR4 and MyD88 in the synovial tissue, key factors in RA-associated immune imbalance. ESP

counteracts this by reducing the nuclear translocation of the NF-κB p65 subunit, inhibiting the TLR4 signaling pathway and modulating the HDAC/TLR4/NF-κB pathway. This reduces the release of inflammatory cytokines, limiting their entry from the intestine into the joints, thereby minimizing joint damage and alleviating RA symptoms (173,174).

Glycosides

Total glucosides of Paeony (TGP). Paeony, a traditional Chinese herbal medicine, is highly regarded for its medicinal properties. TGP, extracted from the roots of paeony, serves as an immunomodulator and is widely used in China for RA treatment. Although clinical studies have not yet conclusively demonstrated that combining TGP with conventional drugs offers superior efficacy in treating RA, they have shown that TGP can mitigate liver function damage caused by drug treatments (175-178). The primary chemical components of TGP include paeoniflorin, albiflorin, hydroxy-paeoniflorin, paeonin and benzoylpaeoniflorin, all of which are monoterpene glycosides with low bioavailability and poor absorption (179,180). These compounds tend to accumulate in the intestine and can be metabolized by the intestinal microbiota (181-183). TGP treatment reduces arthritis severity in CIA rats, restructures the gut microbiota by correcting 78% of differential taxonomic profiles and enriches beneficial symbionts, thereby restoring intestinal ecological balance. Additionally, TGP markedly downregulates intestinal IFN-γ and secretory IgA production, modulates mucosal immunity, induces autoimmune tolerance and suppressed inflammatory responses (180). TGP also inhibits the expression of VEGF in CIA rats, regulating synovial neovascularization and abnormal synovial cell proliferation (184). These findings suggest that the therapeutic effects of TGP on RA may be mediated through intestinal regulatory mechanisms.

Polysaccharides and glycosides of Aralia echinocaulis. *Aralia echinocaulis* (*A. echinocaulis*), an *Aralia* species (Araliaceae), is a medicinal herb primarily found in southwestern China and in Zhejiang and Anhui provinces. Rich in polysaccharides and glycosides, it is commonly used in medicinal wine and has shown therapeutic benefits for RA (185). The total polysaccharide and glycoside (TPG) from *A. echinocaulis* can reduce serum IL-1β and TNF-α levels in CIA rats, alleviate synovial hyperplasia and modulate the gut microbiota composition. KEGG pathway and COG functional analyses reveal that TPG-induced changes in the gut microbiota are linked to the transport and metabolism of coenzymes and nucleotides, which may generate anti-RA metabolites, thereby suppressing CIA. However, TPG from *A. echinocaulis* showed no effect in antibiotic-treated CIA rats, indicating that its anti-arthritic action depends on the regulation of the gut microbiota (186).

Others

Tripterygium hypoglaucum (Levl.) Hutch (THH). THH is a commonly used drug in China, known for its immunosuppressive, anti-tumor and anti-inflammatory properties (187). Numerous studies have demonstrated that THH extract improves joint indices, reduces swelling and mitigates joint damage in RA animal models (188,189). Further investigations have revealed that THH extract markedly elevates the colonic mRNA levels of tight-junction proteins and mucins in RA mice. It also reduces the abundance of pathogenic bacteria, such as *Marvinbryantia*, *Desulfovibrio*, *Parabobacterides*, *Bacteroides* and *Butyricimonas*, while enriching beneficial taxa such as *ifidobacterium*, *Akkermansia*, *Lactobacillus* and *Roseburia*. These alterations help restore microbial balance, reprogram metabolic pathways, enhance SCFA production, and modulate BA metabolism (190,191). Additionally, THH treatment reduces the expression of pro-inflammatory cytokines (IL-1β, IL-8, IL-17) and increases anti-inflammatory cytokine IL-10 in the colon of RA model mice. It also inhibits NLRP3 inflammasome activation and blocks the TLR4/MyD88/MAPK signaling pathways in muscles and plasma, reducing joint inflammation and protecting the joints (190,191). However, these therapeutic effects were not observed in RA mice with gut microbiota deficiency, confirming that a healthy gut microbiota is essential for the therapeutic efficacy of THH extract (190,191).

Radix Toddalia Asiatica (RTA). RTA, a liana primarily found in China and Southeast Asia, has anti-inflammatory and analgesic properties, making it widely used for treating chronic pain and gastrointestinal disorders (192-194). RTA extract reduces serum inflammatory markers in RA model animals, increases chondrocyte survival in inflammatory environments, and improves arthritis symptoms (194-196). Research by Qin *et al* (197) suggests that the therapeutic the mechanism of RTA extract in RA may involve modulating intestinal immune responses and restoring microbial balance. Following RTA treatment, Th17 (IL-17A, RORC, IL-1β and IL-6) and Treg (IL-10 and FOXP3) cell-related protein and mRNA levels in the colon tissues of AIA rats were downregulated and upregulated, respectively, promoting the restoration of the Th17//Treg balance. Additionally, RTA extract reshaped the intestinal microbiota of AIA rats, increasing beneficial bacteria and reducing RA-associated strains, such as *Liilactobacillus* and *Streptococcus*.

Paederia scandens. *Paederia scandens*, a herb native to countries such as China, India and Vietnam, is commonly used to treat rheumatism and digestive tract diseases and is regarded as a safe plant. *In vitro* cell experiments have demonstrated that *Paederia scandens* extract (PSE) reduces the mRNA levels of pro-inflammatory cytokines (IL-6, IL-1β and IL-17) in fibroblast-like synovial cells from patients with RA and inhibits cell proliferation by suppressing the activation of the JAK-STAT pathway (198). *In vivo* studies further confirmed PSE's therapeutic effect on CIA mice, restoring the intestinal microbiota balance disturbed by collagen induction. PSE reduced relative abundance of inflammation-related microbiota, such as *Desulfovibrio*, *Mucispirillum*, *Helicobacter* and *Lachnospiraceae*. However, whether the intestinal regulatory mechanism plays a pivotal role in PSE's treatment of RA remains to be further explored (199).

Arsenic trioxide (ATO). ATO, a compound with a long history of use in treating various diseases, was approved by the U.S. Food and Drug Administration in 2000 for treating acute promyelocytic leukemia, eventually emerging as a cutting-edge treatment for lymphoma, solid tumors, and other conditions (200). Studies suggest that ATO holds potential in RA treatment by balancing immune cells and inhibiting angiogenesis (201-203). Additionally, regulating intestinal

microecology and abnormal metabolites may be part of ATO's therapeutic action in RA (204). Specifically, ATO treatment increased the richness and diversity of the intestinal microbiota in CIA mice, restoring the imbalance between the two major phyla, *Firmicutes* and *Bacteroidetes* (204). On a metabolic level, ATO regulates several metabolites, including (-)-β-pinene, a substrate involved in lipid metabolism related to RA. ATO may alleviate RA symptoms by regulating lipid metabolism through the modulation of (-)-β-pinene levels (204).

Columbianadin. Angelicae pubescentis radix (APR), the dried root of *Angelica pubescens* Maxim. f. *biserrata* Shan et Yuan, has a long history of use in treating rheumatic joint pain. A natural component extracted from APR, columbianadin, exhibits anti-inflammatory, analgesic, and anti-tumor properties (205-208). Columbianadin effectively inhibits the JAK1/STAT3 and NF-κB inflammatory pathways, improves the Keap1/Nrf2 oxidative stress pathway and modulates the expression of inflammatory factors (downregulating IL-1β, TNF-α and IL-6) and antioxidant markers (upregulating glutathione and superoxide dismutase). This results in reduced swelling and joint protection (209). Furthermore, columbianadin restores microbial diversity in the small intestine of CIA mice, modulates energy- and amino-acid-metabolic pathways, and helps maintain micro-ecological homeostasis with minimal adverse effects (209).

5. Conclusion and future perspectives

The 'gut-joint axis' is not exclusive to RA but also occurs in other immune-mediated arthritis diseases, with distinct mechanisms at play. Studies have shown that ~50% of patients with spondyloarthritis (SpA) develop subclinical intestinal inflammation, which can progress to inflammatory bowel disease (IBD), most commonly Crohn's disease (210,211). By contrast, subclinical intestinal inflammation in RA predominantly involves the small intestine and is characterized by lymphocyte and macrophage infiltration (39,210,211). Furthermore, the composition of the intestinal microbiota differs between RA and SpA: *Prevotella* is markedly and specifically enriched in RA, whereas no distinct microbial signature has yet been identified for SpA. However, dysbiosis-driven activation of the IL-23/IL-17 axis plays a pivotal role in the pathogenesis of both SpA and IBD (212). Additionally, whereas $CD4^+$ T cells that dominate the 'gut-joint axis' in RA, $CD8^+$ T cells bearing identical T-cell receptor clonotypes are the predominant immune population in both the gut and joints of SpA patients (210,213).

Overall, alterations in the microbiota are a key factor in the 'gut-joint axis' of RA. These changes not only influence mucosal and systemic autoimmune responses *via* metabolites, molecular mimicry and other mechanisms but are also closely linked to the efficacy and side effects of RA treatments, particularly methotrexate (24,214,215). Research focusing on specific microbiota and metabolomics may offer a more targeted approach to understanding the 'gut-joint axis' in RA. Since the intestinal microbiota is influenced by numerous factors, broadly studying all microbiota changes to pinpoint the pathogenesis of diseases may lead to incorrect conclusions.

Natural compounds possess diverse biological activities and can improve RA by regulating the intestinal microecology. Importantly, the anti-RA effects of certain compounds are dependent on the intestine. The intestinal microbiota represents a potential target for the treatment of RA, particularly with high-molecular-weight and low-bioavailability natural compounds. Although existing reviews have catalogued the potential mechanisms by which natural compounds ameliorate RA and occasionally mention the gut-joint axis, the present review presented a more comprehensive and systematic summary of the anti-RA effects of natural compounds based on this mechanism (216-219). The present review highlighted the protective effects of natural compounds such as alkaloids, polyphenols, polysaccharides and plant extracts on the intestinal mucosa and the regulation of intestinal flora homeostasis in RA model animals, ultimately improving RA symptoms. It explored the anti-RA potential and mechanisms of these compounds, providing a scientific foundation and new insights for the development of novel therapeutic drugs. Several natural compounds have already been widely used in clinical practice, while others, with solid scientific support for drug development, should be prioritized. For example, berberine, a well-studied natural compound, has shown significant therapeutic effects across various diseases, suggesting its broad potential in RA drug development. *Lycium barbarum* polysaccharides, one of the key active components of *L. barbarum*, also exhibit notable efficacy in treating RA. Moreover, *L. barbarum*, being a readily available and low-cost source, could be a valuable candidate for drug development.

Despite their therapeutic potential, most natural compounds suffer from low oral bioavailability and tend to accumulate in the gastrointestinal tract after oral administration. While this accumulation may be advantageous for RA treatment through the 'gut-joint axis' mechanism, improving the bioavailability of these compounds could further enhance their efficacy in disease recovery. Additionally, challenges in translating natural compounds into clinical drugs include structural instability, poor solubility and unclear toxic or side effects. Hence, novel drug discovery remains a protracted, multi-parameter endeavor that demands rigorous, head-to-toe optimization and integrated assessment of all pharmacological, pharmacokinetic and safety attributes. However, as pharmacological mechanisms of natural compounds are being dissected at ever-greater depth, our knowledge of these compounds has broadened and their multifaceted profiles are now improved understood.

At present, new drug delivery methods such as nanoparticles are developing rapidly. It is expected that in the future, there will be more basic research and clinical trials on the treatment of RA using natural compounds through the 'gut-joint axis' pathway. This is precisely what is needed at present.

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WH was responsible for conceptualization, writing the original draft, writing, reviewing and editing. RL was responsible for writing, reviewing and editing and providing illustrations and tables. ZZ was responsible for writing, reviewing and editing. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

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