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Therapeutic mechanisms of polysaccharides in the management of rheumatoid arthritis: a comprehensive review

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Rheumatoid Arthritis (RA) is a chronic autoimmune disease characterized by synovial inflammation and destruction of articular cartilage and bone, which seriously affects patients' quality of life. In recent years, with the in-depth research on natural medicines, the application of polysaccharides in the treatment of RA has gradually gained attention due to their unique bioactive components and diverse pharmacological effects. Polysaccharides were reported to exert anti-inflammatory, antioxidant, immunomodulatory, and protective effects on cartilage and bone tissues. This review briefly introduces RA, its etiology and pathogenesis, and the different sources and structures of polysaccharides. It focuses on the mechanisms of polysaccharides in the alleviation of RA, mainly through the modulation of immune cell function, inhibition of inflammation, regulation of gut microbiota, promotion of bone formation and repair, and influence on related pathways. The aim of this review is to summarize the polysaccharides and their mechanisms of action in the alleviation of RA, with a view to providing new ideas for the clinical treatment of RA.

KEYWORDS

rheumatoid arthritis (RA), polysaccharides, mechanism, immune cells, cytokines

1 Introduction

Rheumatoid arthritis (RA) is one of the most common chronic autoimmune diseases (1). Its pathogenesis involves a complex interaction between abnormal activation of the immune system, inflammatory response and gut microbial homeostasis (2). Epidemiology shows that the global prevalence of RA is about 0.5%-1%, and the incidence in women is 2–3 times higher than that in men, which seriously affects the quality of life of patients (3). Once diagnosed, RA requires lifelong treatment (4). It also brings a heavy economic burden to the society. Currently, the treatment strategies for RA mainly include drug therapy, physiotherapy, surgery (5–8). However, in view of its complex pathogenesis and diverse

clinical manifestations, the search for safer and more effective treatments has always been a research hotspot in the field of rheumatology (9-11). In recent years, polysaccharides, as a class of natural products with a wide range of biological activities, have gradually attracted attention for their potential in alleviating rheumatoid arthritis (12, 13). The aim of this article is to review the role of polysaccharides and their potential mechanisms in the alleviation of RA, with a view to providing new ideas and strategies for the treatment of RA.

Polysaccharides are a class of macromolecular compounds consisting of multiple monosaccharide molecules linked by glycosidic bonds, which are widely found in plants, animals and microorganisms (14-16). Depending on the source, polysaccharides can be classified as plant polysaccharides, animal polysaccharides and microbial polysaccharides (17-19). Polysaccharides have a variety of biological activities, such as immunomodulation, antiinflammatory, antioxidant, anti-tumour (20, 21). These activities are closely related to their complex chemical structures. In recent years, more and more studies have shown that polysaccharides can regulate the immune system, inhibit the inflammatory response, promote tissue repair and other pathways to produce therapeutic effects on a variety of diseases, including rheumatoid arthritis (22, 23). The pathogenesis of RA is complex and involves a variety of aspects, such as genetics, the environment, immunity (24, 25). In the pathogenesis of RA, the immune system is abnormally activated and attacks its own synovium, leading to synovial inflammation and joint damage (26, 27). Synovial inflammation further triggers the formation of pannus, which invade the articular cartilage and bone, releasing a variety of inflammatory mediators and proteases and accelerating joint destruction (28, 29). In addition, RA patients suffer from pathological changes such as enhanced oxidative stress and imbalanced cytokine networks, which together contribute to

disease progression (30, 31). Therefore, therapeutic strategies for RA need to take multiple aspects into account, including inhibiting the inflammatory response, regulating immune balance, and promoting tissue repair (32, 33).

Over the past decade, mentions of polysaccharides and RA increased from 19 in 2015 to 25 in 2024 (Figure 1A). Figure 1B shows the co-occurrence of keywords related to polysaccharides and RA. Among them, there are many keywords related to RA, such as inflammation, Interleukin-6 (IL-6) and B cells. This review provides a reference for further research and application of developing new therapeutic strategies for RA. The aim of this review is to provide a comprehensive overview of current research involving plant polysaccharides, animal polysaccharides and microbial polysaccharides, the therapeutic rheumatological activity of polysaccharides from different sources and their mechanisms, with a particular focus on the relevant signaling pathways for the treatment of RA, NF-KB, PI3K/AKT, JAK/STAT and MAPK. This work also centers around the need for further research to better understand the limitations of clinical therapy with polysaccharides. It also critically examines the challenges associated with its clinical use, especially the safety concerns.

2 Methods

This narrative review searched PubMed, Web of Science, SpringerLink and Science Direct databases using keywords and related terms. It used certain keywords, i.e. polysaccharides and RA, and combined these terms with the following keywords: plant, microorganism, animal, immune, inflammatory, oxidative, bone tissue, pathway, etc. The last search was conducted in March 2025. The language of literature search was English and references were selected based on their relevance. Duplicate studies and irrelevant



In 2022, polysaccharides for RA were published to a near-decade high of 34 articles, and have remained at 25 articles in 2023 and 2024. Thus, research findings on polysaccharides for RA have been of interest

references were excluded, and abstracts of the remaining articles were reviewed to ensure they met the inclusion criteria for the review.

3 RA background

3.1 Etiology and pathogenesis of rheumatoid arthritis

RA is an autoimmune disease that is characterized by focusing on articular cartilage erosion and bone destruction, ultimately leading to joint deformity and loss of function (34). The main clinical manifestations of patients are symmetrical morning stiffness, pain and swelling of multiple joints to varying degrees, accompanied by limited movement, and joint deformity may occur in patients with a longer course of the disease (35, 36). RA-related extra-articular manifestations (EAM) can involve all organ systems, with a wide range of symptoms (37, 38). As shown in Figure 2, in addition to intra-articular manifestations, there may be secondary tissue and organ damage such as cardiovascular, pulmonary, renal, ocular, cutaneous ulcer, digestive and neurological disorders (39). Approximately 17.6 million people worldwide suffer from RA, and more than 3 million are disabled. As the population continues to age, the number of RA cases is projected to reach 31.7 million by 2050, increasing burden on society (39). Epidemiological studies have shown that the prevalence of RA in China is 0.42 per cent, affecting about 5 million people, with a male-to-female ratio of about 1:4 (40).

3.2 The development and pathogenesis of RA

As shown in Figure 3, the pathogenesis of RA is complex and is the result of a combination of factors. An imbalance in the immune system is key. The immune imbalance in rheumatoid arthritis is characterized by T-cell abnormalities and an imbalance of proinflammatory/anti-inflammatory factors that trigger joint destruction (41, 42). Articular cartilage and bone are destroyed by inflammatory mechanisms involving a variety of pro-inflammatory factor-secreting cells, including immune cells (e.g., mast cells, macrophages, dendritic cells, T-cells, and B-cells) and synoviocytes (synovial macrophages (SMs) and fibroblast-like synoviocytes (FLS)) (43). Similarly, inflammatory cytokines play a key role in the development of RA, the synovial inflammatory response and bone destruction (44, 45). Among them, the involvement of TNF and IL-6 is central to the pathogenesis of RA, and other cytokines such as IL-17, IFN-γ, IL-1β, IL-18, and granulocyte-macrophage colonystimulating factor (GM-CSF) also play important roles (46). These cytokines, together with immune cells and autoantibodies, induce and maintain joint inflammation in RA, ultimately leading to cartilage and bone damage in the affected joints (Table 1). RA has



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Synoviocytes, SMs, FLS), Inflammatory Cytokines (TNF and IL-6), Environmental factors (Silica dust, Long-term smoking, Cold and humid environments Exposure to certain chemicals and Other Causes (Gut microbiota, Genetic predisposition, A variety of infections, General endocrine factors) jointly accelerated the development of RA.

a recognized genetic component, and studies have shown that in identical twins, if one twin has RA, the other has a probability of developing the disease of about 15 per cent. Certain genes are associated with the development of RA, such as HLA-DR4, which affects the immune system's recognition and response, increasing the risk of the disease (47). In addition, a variety of infections are associated with the development of RA, such as EBV, Chlamydia pneumoniae, and Helicobacter pylori. Infections may activate the immune system, and some components of pathogens are similar to the body's own antigens, so that the immune system attacks the pathogen by attacking its own tissues by mistake, i.e., a molecular mimicry mechanism (48). General endocrine factors can also trigger rheumatoid arthritis, such as sex hormones. The incidence of RA is higher in women than in men. The risk of RA in women particularly increases during pregnancy, postpartum and around the time of menopause due to hormonal fluctuations (49). Estrogen regulates immune cell function, affects cytokine secretion, alters the immune balance and increases the susceptibility of RA. Lifestyle habits and

environment can trigger rheumatoid arthritis (49). For example, long-term smoking disrupts the immune balance in the lungs and produces inflammatory factors (TNF-α, IL-8, CCL20), increasing the likelihood of RA onset (50). Cold and humid environments can affect blood circulation and immune function, increasing the risk of developing RA (51). Exposure of the body to certain chemicals, such as silica dust, may also trigger RA (52). With advances in highthroughput sequencing, it has been widely recognized that the host microbiota, particularly the gut microbiota, plays a key role in the pathogenesis and progression of RA (53). The gut microbiota and gut-associated lymphoid tissues work together to maintain immune homeostasis within the host and can serve as an indicator of host health status, and if their interactions are disrupted, they can have an impact on mucosal and systemic immunity and lead to the development of a variety of inflammatory and autoimmune diseases (54). Therefore, further elucidation of the pathogenesis of RA and promotion of RA-related drug research are of great significance in improving treatment efficacy of RA.

	Туре	Major role	References
Immune cells	T cells	The CD4+ T cell subset of T cells is the dominant cell type in the pathogenesis of RA. Regulatory T cells and Th17-dominant Th can stimulate the differentiation of a variety of cytokines, and the imbalance of Th1/Th2 and Th17/regulatory T cells is key to the development of RA.	(109)
	B cells	It can activate macrophages and osteoclasts, act as antigen- presenting cells to activate T cells, and secrete autoantibodies and inflammatory factors such as TNF- α , IFN- γ , IL-6, IL-1 β , IL-17, IL- 18, etc.	(110)
	Macrophages	Activatable macrophages drive synovial inflammation by secreting cytokines, and their degree of infiltration in the synovium correlates with the degree of joint erosion.	(111)
	Dendritic cells	Mature dendritic cells effectively activate the initial T cells, which are located at the center of initiating, regulating, and maintaining the immune response.	(112)
	Neutrophils	Release of multiple degradative enzymes, inflammatory factors and reactive oxygen species leads to vascular endothelial dysfunction and tissue damage, and secretion of inflammatory factors such as IL-1, IL-6, IL-12, TGF-β and TNF.	(113)
	Mast cells	It increases vascular permeability, activates synoviocytes, promotes vascular proliferation, and participates in matrix remodeling, which in turn leads to the destruction of cartilage and bone.	(114)
Synovial cells	SMs	A variety of cytokines can be secreted to regulate and mediate immune response processes. They promote inflammatory responses, enhance activation and migration of immune cells, and promote wound healing.	(115)
	FLS	Responsible for producing a variety of cytokines that may significantly reduce inflammation and damage in the joints.	(116)
Cytokines	TNF	TNF inhibitors prevent TNF from binding to its receptor and inhibit the inflammatory cascade, reducing synovial inflammation and joint damage.	(117)
	ІІ6	IL-6 plays a major role in rheumatoid arthritis by mediating the inflammatory response, exacerbating joint damage and promoting the autoimmune response.	(118)
	IL-17	IL-17 synergizes and releases a variety of pro-inflammatory cytokines (e.g., IL-1 β , IL-6, and TNF- α), stimulates a variety of chemokine ligands involved in the formation of vascular opacities, exacerbates synovial inflammation, and destroys articular bone and cartilage.	(119)
	IFN-γ	Regulate the function of T-cells, B-cells and other immune cells, correct immune imbalance, inhibit autoantibody production and abnormal attack of immune cells on joint tissues.	(120)
	IL-1β	IL-1β can be synthesized and secreted by a variety of cells, such as monocyte-macrophages, fibroblasts, B-lymphocytes, natural killer cells, and smooth muscle cells, among which monocyte- macrophages are predominant.	(121)
	IL-18	It plays an important role in the pathogenesis of rheumatoid arthritis by inducing IFN-γ production through multiple pathways.	(122)
	GM-CSF	GM-CSF promotes the activation, differentiation, survival, and proliferation of monocytes and macrophages transported in synovial joints of inflammatory tissue RA, as well as resident tissue macrophages.	(123)

TABLE 1 Multiple immune cells and cytokines play important roles in RA intrinsic and adaptive immunity and its development.

4 Polysaccharide and RA

4.1 Sources of polysaccharides

Polysaccharides are macromolecular compounds consisting of multiple monosaccharide molecules linked by glycosidic bonds and are widely found in living organisms. Depending on the source, polysaccharides can be classified into three main categories: plant polysaccharides, animal polysaccharides and microbial polysaccharides. As shown in Table 2, the preparation, structure, activity, and references of polysaccharides from different origins were listed. In addition, polysaccharides from different sources (plants, animals, microorganisms) exhibit unique mechanisms in RA therapy due to differences in chemical structure and targets of action. Plant polysaccharides are mainly heteropolysaccharides, which often contain hydroxyl and carboxyl groups, have high molecular weights, and some of them have helical conformations (55). Plant polysaccharides can inhibit the autoimmune response of RA by regulating Th17/Treg (56). Animal polysaccharides act directly on the joint microenvironment by virtue of sulfation modification to alleviate acute inflammation and cartilage damage (57). Microbial polysaccharides regulate systemic immune homeostasis through the "gut-joint axis" and are suitable for RA associated with gut dysbiosis (58).

4.2 Mechanisms associated with the alleviation of RA by polysaccharides

Polysaccharides, as natural active ingredients, have a variety of mechanisms of action to alleviate RA, which may provide new ideas for the treatment of RA, such as by regulating immune cell function, inhibiting inflammation, regulating the gut microbiota, promoting bone formation and repair and related pathways (Table 3). As shown in Figure 4, polysaccharides exhibit multiple mechanisms of action in alleviating RA.

4.2.1 Regulation of immune cell function

RA is an autoimmune disease mainly characterized by chronic synovial inflammation, and its pathogenesis is complex, involving the abnormal activation of multiple immune cells and cytokines. In recent years, the role of polysaccharides in the treatment of RA has received widespread attention, and related studies have shown that polysaccharides can attenuate the immune response of RA by regulating the function and number of immune cells and balancing the immune system (59). However, although these studies have provided new ideas for the treatment of RA, there are also some problems that deserve in-depth discussion. Studies have shown that polysaccharides can enhance the activity of Tlymphocytes, B-lymphocytes and natural killer cells (NK cells), and promote the secretion of immune factors, while inhibiting excessive inflammatory responses (60, 61). For example, in a study that included 60 patients with RA and 40 patients with Huntington's disease (HD), the microbial polysaccharide Galactoxylomannan (GalXM) was able to increase the activation of caspase-3 and ultimately increase the rate of apoptosis in T cells subset. GalXM was able to reduce STAT3 phosphorylation, IL-17 production and Th17 cell proliferation. It was also demonstrated that CD45 expression on target T cells was required to mediate the immunomodulatory effects of GAlXM (62). In terms of the studies themselves, most of the existing studies on the mechanisms of polysaccharides in RA therapy have focused on in vitro cellular experiments and animal models and small sample sizes. The limitation of sample size may lead to the bias of research results, and it is difficult to fully reflect the real efficacy and safety of GalXM in RA patients. In addition, there are differences between animal experiments and human physiological environments, and whether the mechanism of action of polysaccharides in animals is fully applicable to humans needs to be further verified (63). Guo et al. (13) prepared a novel self-assembled nanoparticle containing Celastrol (Cel) and matrix metalloproteinase (MMP)-sensitive chemo-acoustic kinetic therapies targeting macrophages at the site of inflammation in rheumatoid arthritis from Achyranthes polysaccharide. The final results show that DS-PVGLIG-Cel&Abps-thioketal-Cur@Cel nanomicelles (DPC&ATC@Cel) has a favorable in vitro and in vivo ability to treat RA with a good in vivo safety profile. Natural polysaccharides such as chitosan, alginate and hyaluronic acid are widely used in RA therapy because they are biocompatible and can be easily functionalized to enhance drug loading and targeting (64). However, in the human body, the targeting of nanoparticles, the in vivo metabolic process, and the safety of long-term use still need to be studied in depth (65). In a review, Ganoderma lucidum polysaccharides (GLP) inhibited the proliferation and migration of synovial fibroblasts (RASF) in RA, modulated pro- and anti-inflammatory cytokines, and reduced synovial inflammation. Secondly, GLP regulates the proliferation and differentiation of antigen-presenting cells such as dendritic cells, inhibits the phagocytosis of monocyte-derived macrophages and natural killer (NK) cells, and regulates the ratio of M1, M2 and related inflammatory cytokines. In addition, GLP produces activities that balance humoral and cellular immunity, such as regulating the production of immunoglobulins, the proliferative response of T and B lymphocytes and cytokine release, thus demonstrating immunomodulatory effects (43).

4.2.2 Inflammation suppression

Polysaccharides have significant anti-inflammatory activity, inhibiting the infiltration of inflammatory cells and the release of inflammatory factors, and reducing joint swelling and pain (66, 67). In a study, different doses of *Angelica sinensis* polysaccharide (ASP) alleviated paw swelling in rat models of collagen-induced arthritis (CIA). Antibody levels in the ASP-treated group also showed varying degrees of reduction. Anti-CII IgG and anti-CII IgG2a levels were reduced in a dose-dependent manner, and ASP reduced the effects of CIA by attenuating TNF- α pro-inflammatory factors (68). In another study, administration of *Lycium barbarum* polysaccharide (LBP) significantly reduced serum IL-1 α , IL-1 β , IL-12, and IL-17 levels and restored and normalized IL-10 levels in a rat model of CIA. LBP reduced pro-inflammatory cytokine levels and restored anti-inflammatory cytokine levels (69).

TABLE 2 Polysaccharides of different origins.

	Origins	Preparation	Structure	Activity	References
Plant	Cynanchum Auriculatum	α-Amylase→glucoamylase→anhydrous ethanol→DEAE Sepharose Fast Flow column→dialysis	The backbone included β -1,4-Manp, β -1,4,6-Manp, β -1,4-Glcp and β -1,4,6-Glcp residues, with branches at the O-6 position of β -1,4,6-Manp and β -1,4,6- Glcp residues, consisting of α -T-Araf, α -1,5-Araf, α - 1,2,5-Araf, α -1,3,5-Araf, T-Xylp,1,4-Xylp, β -T-Manp and β -T-Galp residues.	Immunomodulatory activity	(124)
	Typha angustifolia	DEAE-52 cellulose chromatography	PTA-1 comprises glucose (100%) with α-(1 \rightarrow 3) glycosidic bonds, and PTA-2 comprises glucose (66.7%) and rhamnose (33.3%) formed by β-(1 \rightarrow 3) glycosidic bonds.	Anti- Inflammatory Activity	(125)
	Pumpkin	ethanol/ammonium sulfate system→DEAE cellulose-52 anion exchange chromatography column	The backbone of ATPS-PP-1 comprised of (1→3)- linked-Glcp having branching points at O-3 of (1→3,4)-linked-Glcp with terminal Glcp as side chain. ATPS-PP-2, on the other hand, comprised of 1→Glcp, (1→3)-linked-Galp, (1→6)-linked-Glcp, (1→3,6)-linked-Glcp and (1→4)-linked-Glcp as backbone.	Hypoglycemic Activity	(126)
	Millettia Speciosa Champ	decolorization and deproteinization by AB-8 and Sevag method→DEAE-52 cellulose column→Sephadex G-100 column	The backbones of MSCP1 were composed of 1,4- linked-α-D-Glcp, 1,4-linked-α-D-Xylp and 1,4,6- linked-β-D-Glcp. The branch chain T-linked-α-D- Glcp was confirmed to be attached at C-6 of 1,4,6- linked-β-D-Glcp.	immunomodulatory activity	(127)
	Phragmites rhizoma	Alcohol Precipitation→Sevag method→DEAE-52 cellulose chromatography column→Sephadex G-100 column	Three sugar residues, \rightarrow 3)- β -D-GalpA-(1 \rightarrow , \rightarrow 2, 3)- α -L-Fucp-(1 \rightarrow and α -L-Fucp (4SO3–)-(1 \rightarrow PRP-2	Anti- inflammatory activity	(128)
	Bangia fuscopurpurea	Alcohol Precipitation→neutral protease→DEAE-Sepharose Fast Flow→High-performance gel permeation chromatography (HPGPC)→Gas chromatography-mass spectrometry	Repeating 5- α -l-Araf-1 \rightarrow (4- α -d-Glcp-1)4 \rightarrow 4,6- β -d- Manp-1 units, and the side chains consisted of repeating β -d-Galp-1 \rightarrow (4- β -d-Galp-1)4 \rightarrow 4,6- β -d- Galp-1 \rightarrow 3,4- α -l-Rhap, β -l-Arap-1 \rightarrow (3- β -d-Galp-1) 3, and β -l-Arap-1 units	Antitumor activity	(129)
Animal	Hemicentrotus pulcherrimus	distilled water→papain and Sevag reagent→DEAE-52→Sepharose CL-2B	featuring a linear backbone of 1,4-linked α -d-glucose with 1,6- α -d-glucose and 1,6- α -D-glucuronic acid side chains grafted on the backbone in an alternating pattern	Antitumor activity	(130)
	Holothuria nobilis	anion-exchange FPA98 resin column→HPGPC→Sephadex G25 column→Superdex peptide 10/300 GL column→Dionex IonPac TM AS11-HC column	$\label{eq:4} \begin{array}{l} \label{eq:4} & \{4\} - [d-GalNAcR1 - (\alpha 1,2) - l-Fuc3S - (\alpha 1,3) -] - d-GlcUA - (\beta 1,3) - d-GalNAc4S6S - (\beta 1, m - \{4\}) - [l-FucR2 - (\alpha 1,3) -] - d-GlcUA - (\beta 1,3) - d-GalNAc4S6S - (\beta 1, n - 1) - [\beta 1, m - 1) - [\beta 1, m - 1] - $	Anticoagulant and anti-iXase activities	(131)
	Lysastrosoma anthosticta	Gas liquid chromatography of alditol acetates→Gel chromatography→Sephadex G-15 column	$[\rightarrow 3)\text{-}\beta\text{-}D\text{-}GalNAc4S\text{-}(1\rightarrow 4)\text{-}\alpha\text{-}L\text{-}IdoA2S3S\text{-}(1\rightarrow]n$	Anticoagulant activity	(132)
	Mussel			Antioxidant activity	(133)

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(Continued)

TABLE 2 (Continued
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	Origins	Preparation	Structure	Activity	References
		Enzymatic→anhydrous ethanol→DEAE Sepharose Fast Flow→Polysaccharide gel purification system→HPGPC	\rightarrow 4)- α -D-Glcp-(1 \rightarrow , and the end group α -D-Glcp- (1 \rightarrow and α -D-Glcp-(1 \rightarrow 6) - α -D-Glcp- (1 \rightarrow pass \rightarrow 4,6)- α -D-Glcp-(1 \rightarrow		
_	Coelomactra antiquata	Enzymatic hydrolysis \rightarrow Ion exchange \rightarrow Ethanol precipitation \rightarrow HPGPC	$ \begin{array}{l} \rightarrow 4) \cdot \alpha \text{-IdoA2S-}(1 \rightarrow 4) \cdot \alpha \text{-GlcNS3S6S(or GlcNS6S)-} \\ (1 \rightarrow 4) \cdot \beta \text{-GlcA-}(1 \rightarrow 4) \cdot \alpha \text{-GlcNS6S} \text{ (or } \\ \text{GlcNAC)-}(1 \rightarrow 4) \text{-} \alpha \text{-} \text{GlcNS6S} \text{ (or } \\ \end{array} $	Anticoagulant and Fibrinolytic Activities	(134)
Microorganism	Ganoderma lucidum spore	Alcohol Precipitation $\rightarrow \alpha$ -Amylase \rightarrow Chromatography \rightarrow Desalination	$ \begin{array}{l} \mbox{Glc-}(1 \rightarrow 3)\mbox{-}Glc-}(1 \rightarrow 3)\mbox{-}Glc-}(1 \rightarrow 6)\mbox{-}Glc-}(1 \rightarrow 6)\mbox{-}Glc-}(1 \rightarrow 6)\mbox{-}Glc-}(1 \rightarrow 6)\mbox{-}Glc-}(1 \rightarrow 3)\mbox{-}Glc-}(1 \rightarrow 3)$	immunomodulatory activity	(135)
	Flammulina velutipes	Alcohol Precipitation→anhydrous ethanol, acetone, and petroleum ether→Sevag reagent and dialysis bags→DEAE-52 cellulose column→Sephadex G-100 column	CHFVP-1: the backbone of \rightarrow 6)- α -D-Galp-(1 \rightarrow and the branch of Galp by an \rightarrow 3,6)- α -D-Manp-(1 \rightarrow attached with T- β -D-Glcp or t- α -L-Fucp side chains. CHFVP-2: the construction of \rightarrow 6)- β -D-Glcp-(1 \rightarrow and T- β -D-Glcp.	Coagulant activity	(136)
	Cordyceps militaris (L.) Link	NaOH→HCl→cellulose membrane→Q-Sepharose TM Fast Flow column→ Sephacryl S400HR column	CM3I: composed of→4)α-D-Glcp(1→glycosyls and differed from starch due to the presence of→4,6)β- D-Glcp(1→glycosyls. CM3II: composed of →4)-β- D-Manp(1→6)-α-D-Manp(1→6)-β-D-Manp (1→linked glycosyls, and especially the presence of O-methyl.	Anti- atherosclerotic activity	(137)
	<i>Ramaria flaccida</i> (Fr.) Quél	Alcohol Precipitation→DEAE-52 cellulose column→GC-MS	The main chain of RF–1 consisted of $(1\rightarrow 6, 2)$ $-\alpha$ –D–galactopyranose and $(1\rightarrow 6, 4)-\alpha$ –D –glucopyranose. One of the branched chains was linked to 4–O of the main glucose chain by $(1\rightarrow 6)$ $-\alpha$ –D–glucopyranose and next linked by one $(\rightarrow 4)$ $-\beta$ –D–glucopyranose. The other two branched chains were both linked to 2–O of the main glucose chain by one $(\rightarrow 4)$ – β –D–glucopyranose.	Antitumor activity	(138)
	Boletus reticulatus Schaeff	Alcohol Precipitation→DEAE cellulose→Dialysis→HPGPC→HPLC→GC-MS	1,6-linked α-D-galactose and 1,2,6-linked α-D- galactose which branches were mainly composed of a terminal 4-linked β-D-glucose	Antitumor activity	(139)

TABLE 3	Experimental	models	of	rheumatoid	arthritis.

Polysaccharides		Model	Dose	Mechanisms	Reference
Ephedra sinica	pure polysaccharide ESP-B4	a Freund's complete adjuvant (FCA)-induced RA model in rats; THP-1 cells, RAW264.7 cells and PBMC cells	200 and 100 mg/ kg/day	ESP-B4 significantly improves all parameters of inflammation. Treats RA by inhibiting the TLR4 signaling pathway, which reduces the release of inflammatory factors and cytokines.	(140)
Angelica sinensis	Angelica sinensis polysaccharide ASP-2pb	type-II collagen induced arthritis (CIA) modeling	400 mg/kg	ASP-2pb affects specific gut bacteria as well as metabolites produced by gut bacteria in the process of alleviating RA.	(141)
Anoectochilus roxburghii	ARP	CIA mouse model	120 mg / kg	ARP significantly inhibited the activation of the NF- κ B pathway by inhibiting the phosphorylation of I κ B and p65, thereby down- regulating the mRNA expression of IL-1 β and IL-6 in LPS.	(142)
Holothuria leucospilota	Holothuria leucospilota polysaccharides (HLP)	intraperitoneally immunosuppressive model	80 mg/kg	HLP improves the immune factors, T-cell markers, and Toll-like receptors (TLR) pathway-related proteins expression. HLP increases the short-chain fatty acids concentration and regulates the gut microbiota composition.	(143)
Streptococcus pararoseus	Streptococcus pararoseus polysaccharide (SPP)	CIA mouse model	400 mg/kg	The SPP intervention increased the relative abundance of beneficial bacteria that have the potential to degrade fungal polysaccharides or produce short-chain fatty acids.	(144)
Wu- tou decoction	Wu-tou decoction polysaccharides (PS)	a model of adjuvant-induced arthritis (AIA) in rats	9.8 g crude drug/ kg/day	PS may be able to control the disruption of the intestinal microbiota and improve the intestinal environment in model animals, thereby influencing the absorption and metabolism of SM	(145)
	Gelatin	Raw264.7 cells and chondrocyte cells	Gelatin as a carrier	Gel/FA-PDA@Leon hydrogel inhibits inflammatory responses and protects chondrocytes from ferritin phagocytosis/iron death by down-regulating the JAK2/STAT3 signaling pathway in macrophages.	(146)
	chitosan	a FCA-induced RA model in rats	20 mg/kg	Chitosan nanoparticles (Q-NPs) containing quercetin significantly reduced ankle diameter, oxidative stress markers, and inflammatory cytokines such as TNF-α and IL-6.	(147)
	chondroitin sulfate	Caudal intradermal injection of heat inactivated Mycobacterium tuberculosis incomplete Freund's adjuvant suspension	300 mg/kg	Chondroitin sulfate with glucosamine significantly reduced paw swelling and inflammatory markers while altering intestinal flora by inhibiting LPS-producing bacteria and the TLR-4/NF- κB pathway.	(148)

Lonicerae Japonicae Caulis polysaccharide (LJCP-2b) is a homogeneous heteropolysaccharide. Its structure mainly consisted of 1,3,6-β-D-Galp, 1,4-α-D-Glcp, 1,4,6-α-D-Glcp, 1,4-β-D-Galp, 1,2,4-α-L-Rhap and 1,4-α-D-GalpA. In vitro experiments demonstrated that LJCP-2b affected TNF-\alpha-induced rheumatoid arthritis fibroblast-like synoviocyte (RA-FLS) functions, including attenuation of cell viability, increase in apoptosis, decrease in the number of migratory movements and adhesion capacity, and reduction in the levels of IL-6 and IL-1β. These results suggest that LJCP-2b has the activity to inhibit RA-FLS hyperproliferation and inflammatory response (70). Glycosaminoglycans (GAG) play a crucial role in the pathophysiology of RA (71). One of the main pathways by which these long-chain polysaccharides in the extracellular matrix and on the cell surface interact with growth factors, cytokines, and proteases that influence cell behavior is the TGF- β (transforming growth factor- β) signaling pathway, where GAGs enhance the anti-inflammatory effects of TGF-B, promote the differentiation of regulatory T-cells (Tregs), and inhibit proinflammatory cytokine production (72). In addition, Sun et al. extracted polysaccharides with anti-inflammatory activity from Large-leaf Yellow tea (LYT) and identified the presence of β -d- $Xylp(1 \rightarrow, \rightarrow 2, 4)$ - β -d- $Xylp(1 \rightarrow, \rightarrow 3)$ - β -d-Manp(1 \rightarrow, \alpha-d-Glcp $(1 \rightarrow and \rightarrow 2, 4)$ - α -d-GalAp $(1 \rightarrow linkages.$ They found that LYT polysaccharides inhibited the migration and proliferation of MH7A cells and reduced NO production in a $\text{TNF-}\alpha\text{-induced}$ inflammation model. NO regulates the production of a variety of inflammatory factors, and its reduced production can upset the balance between pro- and anti-inflammatory factors, leading to difficulty in effectively controlling the inflammatory response and affecting immune homeostasis. The abundant presence of xylose accounts for 39% of the polysaccharide structure of LYT, and its unique linkage pattern ($\rightarrow 2$, 4)- β -d-Xylp(1 \rightarrow) appears to be a major contributor to its anti-inflammatory effects (73). Lin et al. introduced an alginate nanogel embedded in liposomes designed to enhance in vivo stability while retaining the inherent benefits of liposomes for RA. By incorporating an alginate network, the



liposomes showed increased stiffness, reduced drug leakage, and improved cellular uptake by inflammatory macrophages. In addition, the encapsulated anti-inflammatory chlorogenic acid significantly inhibited ROS production and inflammatory response in arthritic rats, resulting in better therapeutic efficacy (74). Existing studies have relied on the CIA model, which mimics the acute inflammatory response but is fundamentally different from the chronic, progressive synovial lesions of human RA (75). The collagen-induced arthritis (CIA) model involves both cellular (particularly Th17-mediated) and humoral immune responses, and its inflammatory microenvironment involves more complex cellcell interactions (76). Furthermore, whether the structural complexity of polysaccharides acts through multi-target regulation remains to be systematically evaluated.

4.2.3 Ameliorating gut microbiota and its metabolites

Gut microbiota as one of the factors that can directly influence the body's immune response, the role of gut microbiota in the field of RA has been gradually explored (77). Improving the gut microbiota and its metabolites can jointly have an impact on the development of diseases such as RA. Regulating the intestinal microbiota to restore its balanced state, as well as improving the composition and level of metabolites, can reduce the release of proinflammatory factors, inhibit the activation of inflammatory vesicles, etc., thereby alleviating the inflammatory response, relieving the symptoms of RA, and playing a protective role for the body (58). Some studies have shown that probiotics such as Lactobacillus reuteri can improve the symptoms of RA, which can be a promising novel target, with the 'gut-joint' axis as an important potential mechanism. The gut-joint axis refers to the stable, bidirectionally regulated interaction between the gut microbiota and the joints. Imbalances in the intestinal microbiota can affect the development of joint diseases such as RA. At the same time, joint diseases also change the structure and function of the gut microbiota (58, 78, 79). In the intestinal microbiota of RA patients, there is a significant increase in the abundance of pathogenic bacteria such as Ruminococcus gnavus group and a decrease in beneficial short-chain fatty acid (SCFAs) producing bacteria such as Roseburia, and these microbiota imbalances promote IL-6 by impairing antioxidant capacity, $TNF-\alpha$ and other pro-inflammatory factors release, exacerbating the development of RA (80). In addition, gut microbiota metabolites such as trimethylamine oxide (TMAO) in RA patients may promote synovial inflammation by activating NLRP3 inflammatory vesicles (81). For example, polysaccharides from Dianbaizhu (DBZP) treatment can affect the abundance of several specific bacteria in CIA mice, such as Lactobacillus, Anaplasma spp. Alistipes, Enterorhabdus, Mucispirillum and Candidatus_Saccharimonas, as well as a number of fecal or urinary Metabolites, such as 11βhydroxytestosterone, pregnanediol 3-O-glucuronide, p-cresol sulfate and several amino acids and peptides, were also altered.

The results suggest that DBZP has a protective effect on CIA in mice by modulating the gut microbiota (82). Linear discriminant analysis Effect Size (LEfSe) is one of the core tools for microbiome research by integrating non-parametric tests and effect size analysis to efficiently identify biomarkers of intergroup differences. In addition, researchers identified 12 bacterial strains enriched in Acanthopanax senticosus polysaccharide (ASPS)-treated mice and 2 strains enriched in CIA mice after initial immunization by LEfSe analysis. ASPS treatment significantly reversed the trend of increased abundance of Bacteroides and the ratio of Bacteroidota/ Bacillota induced by the progression of arthritis. Similar results were observed at the class, order, and family levels finding Acetatifactor, Ruminalococcus, Colidextribacter, Blautia, and were significantly enriched at the genus level in ASPS-treated mice (83). The "gut-joint axis" theory of RA reveals that intestinal microbiota are involved in the pathogenesis of joint inflammation through bidirectional regulation, and polysaccharides have been shown to alleviate the symptoms of RA in mouse models by remodeling the structure of intestinal microbiota and metabolites (84). However, there may be fundamental differences in the regulatory targets of polysaccharides on different host microbiota. Different polysaccharides are preferentially degraded by specific groups of bacteria due to differences in glycosidic bond type and branching structure (85). Segatella copri is a bacterium widely found in the human gut (86). A variety of lactic acid bacteria convert primary bile acids to secondary bile acids via bile salt hydrolases, which activate farnesoid X receptor (FXR) and inhibit intestinal Th17 cells (87). Segatella copri lacks Bile Salt Hydrolase (BSH) activity and is unable to participate in bile acid metabolism. However, its overproliferation may indirectly weaken the anti-inflammatory pathway by decreasing the metabolic substrate for beneficial bacteria through consumption of bile salts (88). In addition, excessive inhibition of Bacteroides may affect dietary fiber metabolism, and enrichment of Lactobacillus may increase the risk of bloating in patients with irritable bowel syndrome (89). Therefore, future assessments regarding the intestinal tolerance of polysaccharide interventions need to be focused.

4.2.4 Promotes cartilage and bone tissue repair

At the same time, polysaccharide can also intervene in the core signaling axis of RANKL/OPG (Key factor in the regulation of bone metabolism), remodel the microenvironment of immune-bone metabolism interaction to regulate the function of osteoclasts and osteoblasts, maintain the balance of bone metabolism, and promote the repair and regeneration of bone tissue (90). At the same time, polysaccharides can also regulate the functions of osteoclasts and osteoblasts, maintain the balance of bone metabolism, and promote the repair and regeneration of bone tissue (91). Ma et al. found that Ephedra sinica polysaccharide (ESP) treatment attenuated the significant infiltration of inflammatory cells, fibroblast proliferation and neovascularization, unevenness of articular cartilage surfaces, localized vascular shadowing, and damage to articular cartilage surfaces, and poorly defined borders of cartilage and subchondral tissues in ankle joints of mice in the CIA group (92). Similarly, the expression of osteogenesis-related genes (ALP and RUNX2) was significantly upregulated by Sporidiobolus pararoseus polysaccharides (SPP), which is essential for osteoblast differentiation and bone formation. On the other hand, the bone remodeling signaling pathway was stimulated by SPP, which significantly reduced the RANKL/OPG ratio and TRAF6 (Tumor necrosis factor receptor-related factor 6) expression, indicating reduced osteoclast activity and differentiation (93). The chemical structures of polysaccharides in the existing studies were roughly analyzed, such as the monosaccharide composition of ESP and the conformational relationship between bone protective activity were not clarified, and different extraction processes may lead to differences in the degree of sulfation modification (94), which directly affects its binding ability to RANKL. In addition, most of the trials in the efficacy assessment indexes were based on histopathologic scores. In contrast, human RA needs to be assessed by imaging hard endpoints for bone protection, such as X-ray Sharp score and MRI bone marrow edema score, which were completely missing in the existing studies.

4.2.5 Polysaccharides alleviate RA through related signaling pathways

As shown in Figure 5, polysaccharides inhibit the activation of inflammatory signaling pathways such as NF-KB, PI3K/AKT, JAK/ STAT and MAPK, and reduce the expression and release of inflammatory factors. By inhibiting the activation of inflammatory signaling pathways, polysaccharides reduce the inflammatory response of synovial tissues, thus alleviating the symptoms of RA. The occurrence of RA is closely related to the dysfunction of NF - κ B, and the expression level of NF - κ B in the lesion synovial tissue of RA patients is significantly increased. Highly activated NF - KB induces the production of various proinflammatory cytokines (such as TNF - α , IL-1 β and IL-6), and the pro-inflammatory cytokines regulate the activation of NF - KB through positive feedback, forming a vicious cycle to aggravate the progression of RA. Relevant studies have shown that the development of RA is closely related to NF-KB dysfunction, and the expression level of NF-κB is significantly elevated in the lesional synovial tissues of RA patients (95, 96). Highly activated NF-KB induces the production of various pro-inflammatory cytokines, such as tumour necrosis factor α (TNF- α), interleukin 1 β (IL- 1β), and IL-6, accelerating the progression of the disease. The upregulation of pro-inflammatory cytokines can in turn regulate the activation of NF-KB through positive feedback, forming a vicious circle and aggravating the progression of RA (97, 98). GAGs affect the Wnt/β-catenin pathway, which is essential for cartilage homeostasis and repair (99). GAGs are involved in the NFκB signaling pathway, which reduces the activation of proinflammatory mediators, such as TNF- α and IL-1 β , which both play a central role in RA. For example, administration of Astragalus polysaccharide (APS) to CIA rats reversed the expression levels of NF- κ B-p65 and I κ B α , thereby blocking the harmful feedback and loop (increase in pro-inflammatory cytokines-activation of NF-κB signaling→induced release of pro-inflammatory cytokines) (100). Similarly, Researchers investigated SD-a from Saposhnikovia divaricata (Trucz.) Schischk and investigated the molecular



to the receptor activates JAK, which in turn catalyzes STAT phosphorylation, and the phosphorylated STAT forms a dimer that enters the nucleus to regulate gene expression. In the MAPK (including JNK, ERK, and P38) signaling pathway, upstream growth factors bind to the receptor to phosphorylate SHC, recruiting GRB2 and SOS. SOS prompts activation by exchanging Ras-bound GDP for GTP. Activated Ras activates Raf1 (a MAP3K), MAP3K activates MEK1 (MAP2K), and MEK1 phosphorylates ERK1/2 (MAPK). ERK enters the nucleus and regulates gene expression, while JNK and P38 function through a similar cascade. Image created with BioRender.com, with permission.

mechanism of the anti-rheumatoid effect of SD-a in a rat model of CIA. The results showed that SD-a could inhibit the significantly elevated expression of TLR4 and TRAF6 proteins in the CIA group, and significantly inhibited the phosphorylation of I κ B- α and the nuclear translocation of NF- κ B p65 (101). Chitosan reduces the expression of cytokines such as TNF- α , IL-1 β and IL-6, which are central to the pathogenesis of RA, by inhibiting NF- κ B activation (102).

The JAK/STAT pathway is one of the important signal transduction pathways of cytokines, regulating the growth, activation, differentiation, apoptosis and functions of cells. In the hematopoietic tissues of RA patients, JAK3, STAT and phosphorylated STAT are mainly highly expressed in activated T cells, B cells and FLS in the synovial lining layer. Chitosan also affects the JAK/STAT signaling pathway by modulating Janus kinase (JAK) activity, thereby reducing downstream transcription

of inflammatory mediators (103). It has been reported that the phosphorylation levels of IKB and p65 in the NF-KB pathway in synovial tissues of CIA mice in the model group were increased to a very high level, whereas the phosphorylation levels in the Dendrobium huoshanense stem polysaccharide (cDHPS)-L group and the cDHPS-H group were reduced by 0-70%, respectively. 30-70%, respectively. Similarly, cDHPS also significantly reduced the elevated phosphorylation of JNK, p38, ERK1/2, PI3K, AKT, JAK1 and STAT3 in a dose-dependent manner in CIA mice. Apparently, cDHPS significantly inhibited the phosphorylation of IkB, p65, JNK, p38, ERK1/2, AKT, PI3K, JAK1 and STAT3 in CIA mice (104). The MAPK pathway, which contains components of JNK, p38, and ERK1/2, plays an important role in RA pathogenesis. In addition, chitosan has been shown to modulate the mitogenactivated protein kinase (MAPK) pathway, which influences cell proliferation, differentiation, and cytokine release in synovial tissue.

This characteristic of chitosan oligosaccharides may have a potential adverse effect on bone homeostasis (105).

RANKL was abundantly expressed in the joint cavity of RA patients and combined with RANK on the surface of osteoclasts and osteoclast precursor cells, inducing the proliferation and differentiation of osteoclast precursor cells, increasing the activity of osteoclasts, and promoting bone resorption, as well as inhibiting the differentiation and function of osteoblasts. For example, the intervention of SPP significantly reduced rheumatoid factor, M1 macrophage activation and pro-inflammatory factors in CIA mice. Comprehensive metabolomics and gene expression analyses showed that SPP alleviated RA through arachidonic acid metabolism and OPG/ RANKL/TRAF6 signaling pathway, played a key role in regulating metabolism and osteoblastic/osteoclastic gene expression in RA progression, and stimulated osteogenic remodeling (93). An in vitro and in vivo study of the therapeutic effects of ASP on RA showed that ASP inhibited TNF-\alpha-induced phosphorylation of components of the JAK2/STAT3 and MAPK signaling pathways in CIA-FLS cells.ASP also inhibited inflammatory cytokine invasion and secretion via JAK2/ STAT3 and MAPK signaling by FLS cells from CIA rats (106).

Existing studies have shown that polysaccharides often act through non-specific inhibition of multiple pathways, such as cDHPS, which simultaneously inhibits NF- κ B-p65 nuclear translocation, JNK/p38/ERK phosphorylation and JAK1/STAT3 activation (104). However, the NF- κ B pathway not only mediates inflammation, but also participates in apoptosis, and long-term inhibition may increase the risk of infection and tumor (107). The overall protein phosphorylation levels (p-NF- κ B-p65, p-STAT3) in synovial tissues were mostly detected by Western blot in animal experiments, but there was a significant heterogeneity in pathway activation among different cell subpopulations in the synovial membranes of human RA (108).

5 Limitations

The review of the role and mechanisms of polysaccharides in the alleviation of RA does have some limitations. As a class of complex biomolecules, the specific mechanisms of action of polysaccharides have not been fully elucidated. Although some studies have shown that polysaccharides possess biological activities such as anti-inflammatory, antioxidant, and immunomodulatory activities, the specific mechanisms of these effects in RA still need further investigation. Therefore, this evaluation may not be able to elaborate in detail and accurately on the mechanism of action of polysaccharides in the treatment of RA in vitro and in vivo (in mice and humans). In addition, due to the differences in experimental conditions, animal models, polysaccharide sources and extraction methods, the experimental data derived from different studies may differ significantly. This makes it challenging for reviews to integrate and analyse these data and to draw consistent conclusions. Currently, polysaccharide studies have shown some efficacy in the animal and in vitro experimental stages, but the effects in clinical applications still need to be further verified.

6 Prospects and future directions

In the therapeutic exploration of RA, polysaccharides have demonstrated multifaceted potential and promise. In the field of targeted delivery systems, polysaccharides can deliver drugs directly, which not only ensures the sustained release of drugs, but also reduces the frequency of local drug delivery and toxic side effects, improves therapeutic safety, and provides a new idea for the development of highly efficient and low-toxicity drug delivery systems. In terms of synergistic combination therapy, dexamethasone in combination with hyssop polysaccharide has been shown to have better therapeutic effects on rheumatoid arthritis than either drug alone, reducing pathological symptoms, improving osteoporosis, and restoring athletic ability, which suggests that the combination of polysaccharides and other drugs is expected to play a synergistic role in providing a better solution for clinical treatment. In addition, in-depth investigation of the role of the gut microbiota-joint axis in the pathogenesis and therapeutic response of RA is also an important direction for the future. Studies have shown that intestinal microbiota dysbiosis is closely related to the development of RA, and polysaccharide vaccines can regulate the intestinal microbiota, maintain the homeostasis of intestinal microbiota, and prevent the autoimmune response caused by intestinal microbiota dysbiosis. Perhaps in the future, based on the modulation of the gut microbiota by polysaccharides, precise therapeutic strategies targeting the gut microbiota-joint axis could be developed. At present, no public information on ongoing clinical trials of polysaccharide in the treatment of RA has been retrieved, but as the research on polysaccharide in the treatment of RA continues to deepen, it is expected that more clinical trials will be conducted in the future to further validate the safety and efficacy of polysaccharide in the treatment of RA, and to promote the development of polysaccharide from basic research to clinical application, which will bring a new hope of treatment to the majority of patients with RA.

7 Conclusions

Polysaccharides, as a class of natural active ingredients, have shown therapeutic potential to alleviate RA by modulating immune responses, inhibiting inflammation, combating oxidative stress and promoting articular cartilage repair. However, the evidence for their use as stand-alone therapies is insufficient, and they are more often used as a complement to conventional therapies to synergize with mainstream drugs. In clinical application, it is necessary to strictly evaluate the patient's condition, including metabolic status and intestinal microecology, to avoid blindly replacing standardized therapeutic regimens.

Author contributions

WL: Writing – original draft, Conceptualization. YK: Writing – original draft, Conceptualization. XW: Writing – original draft. YY: Writing – review & editing. QY: Writing – original draft, Visualization. ZL: Supervision, Funding acquisition, Writing – review & editing.

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