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Potential Effects and Mechanisms of Whole Grain Intake on Rheumatoid Arthritis

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ABSTRACT: As a chronic inflammatory and autoimmune disease, rheumatoid arthritis (RA) leads to joint dysfunction and deformities due to joint inflammation, bone erosion, and cartilage destruction, potentially resulting in permanent disability, which significantly reduces patients' quality of life. Compared with refined grains, whole grains retain components such as the endosperm, germ, and bran, which are rich in higher levels of phytochemicals and nutrients. Recent studies suggest that the components in whole grains may play essential roles in the alleviation of RA. This review summarizes the potential effects of whole grain ingredients on alleviating RA via the inhibition of synovial fibroblast migration, cartilage degradation, and osteoclast activity and further elaborates their mechanisms that phytochemicals and nutrients in whole grains inhibit RA via anti-inflammatory, antioxidant, and immune system modulation pathways. We anticipate that nutritional interventions with whole grains may offer new avenues for the prevention and treatment of RA.

Keywords: Whole grains; Rheumatoid arthritis; Anti-inflammation; Immunomodulation; Antioxidant

1. Introduction

Rheumatoid arthritis (RA) is a chronic systemic autoimmune inflammatory disease that affects small joints, spreads to large joints gradually, and subsequently leads to joint dysfunction and disability, often accompanied by various organ complications, which dramatically reduce quality of life [1]. The global prevalence of RA is increasing, affecting approximately 1% of the population [2]. According to the World Health Organization, as of 2019, approximately 18 million people were affected by RA globally. In addition, the incidence of RA both in China and worldwide is increasing annually [3]. In particular, mainland China reports an incidence rate of 0.42%, impacting a total affected population of approximately 5 million, and this incidence has exhibited an increasing trend [4]. In terms of sex, women face a significantly greater risk of developing RA than men do, with a male-to-female ratio of 1:4 [5]. Regarding the age of onset, the majority of patients are between the ages of 40 and 70 [6,7]. Furthermore, people with obesity and metabolic disorders

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such as hypertension, dyslipidemia, and insulin resistance [8] are at increased risk of RA. In addition, individuals with immune system disorders, chronic kidney disease, chronic obstructive pulmonary disease, and other chronic lung diseases also face a high probability of contracting RA [9-12]. Given the current background of global aging and the high incidence of basic diseases among middle-aged and elderly people, there is an urgent need to improve the treatment and prevention strategies for RA.

Currently, the main drugs used in the clinical treatment of RA include nonsteroidal anti-inflammatory drugs, glucocorticoids, and disease-modifying antirheumatic drugs [6]. Nonsteroidal anti-inflammatory drugs exert anti-inflammatory and analgesic effects by inhibiting prostaglandin production [1], whereas glucocorticoids reduce joint destruction via decreasing proinflammatory cytokines [13]. However, patients with RA may be troubled by the side effects of both drugs, including a series of gastrointestinal adverse reactions [2], osteoporosis, hypertension, and adrenal axis suppression [14]. Disease-modifying antirheumatic drugs, including methotrexate, thalidomide, and bucillamine, constitute another group of drugs for RA treatment that contribute to alleviating the symptoms of RA by inhibiting lymphocyte proliferation and reducing the production of cytokines and antibodies, etc. [15], and also have adverse effects, such as vomiting, rash, leukopenia, impaired liver and kidney function, diarrhea, and increased total serum cholesterol [16,17]. Moreover, since there is still no cure for RA, patients have to take medication continuously or intermittently for a long time to control their symptoms [1], which greatly increases the social and financial burden. Therefore, it's an emergency to develop better treatments for RA. Recent studies suggest that dietary modulation may be a more cost-effective, simple, practical, and acceptable alternative way to relieve RA [18], and up to 40% of RA patients agree that diet significantly affects the onset of the disease [19].

In recent years, whole grains have received increasing attention. Whole grains refer to grains that have not undergone refined processing or have undergone only minimal processing, retaining parts such as the endosperm, germ, and bran, and thus contain various bioactive substances and nutrients compared with refined grains [20]. In particular, whole grains are rich sources of phytochemicals [21,22], dietary fiber (DF) [23], vitamins [24,25], β-glucans [26], and minerals [27], and have shown significant immunomodulatory effects and anti-inflammatory and antioxidant properties. For example, bioactive compounds, such as ferulic acid (FA) and p-coumaric acid (PCA), exhibit a variety of biological activities, especially antioxidative and anti-inflammatory activities, and have shown to be effective in various animal models of diseases, including RA [28]. Furthermore, DF in whole grains plays an essential role in regulating microbiota through the production of short-chain fatty acids (SCFAs), resulting in improved metabolism and immune status [29]. vitamin E acts as a free radical scavenger that protects biological membranes from lipid peroxidation [30], whereas B vitamins serve as coenzymes that support cellular physiological functioning, and deficiency of B vitamins may lead to physical, neurological and psychological symptoms, including disorders of the immune system, weakness, and fatigue [31]. Moreover, both clinical trials and preclinical studies have shown that incorporating whole grains into the diet as part of a balanced and nutritious approach has potential benefits for individuals with RA [32,33]. In this review, we summarize the evidence for the connection between whole

grains and RA management and further explore the potential roles of nutrients and bioactive substances in whole grains in the pathogenesis of RA, providing a deeper understanding and scientific basis for prevention and treatment strategies for RA.

2. Pathogenesis of RA

The typical clinical manifestations of RA include joint pain, stiffness, swelling, and eventual destruction of the joint structure. Although the exact mechanism of RA has not been fully understood, inflammation caused by immune cells, such as macrophages, dendritic cells (DCs), mast cells, natural killer (NK) cells, and T lymphocytes, has been considered as a trigger and primary feature of RA, which subsequently leads to pathological changes in local tissues of joints [34,35].

Among them, macrophages abundantly infiltrate at the interface of the inflamed synovium and cartilage-pannus in RA patients, with the proportion of M1 (proinflammatory) macrophages greater than that of M2 (anti-inflammatory) macrophages, exhibiting extensive proinflammatory destruction and antiapoptotic capabilities [36,37]. Furthermore, neutrophils are recruited into synovium, generate reactive oxygen species (ROS), and trigger oxidation, leading to endothelial dysfunction and tissue damage [38]. Activated neutrophils also secrete immune mediators such as interleukin (IL)-1, IL-6, IL-12, transforming growth factor (TGF)-β, and tumor necrosis factor (TNF)-α, contributing to further inflammation and destruction within the synovial space [39]. In particular, it has been recently found that activated neutrophils interact with fibroblast-like synoviocytes (FLSs) in the synovium to endow them with antigen-presenting cell capabilities and an inflammatory phenotype, and further exacerbates local inflammatory response [40]. As another class of innate immune system cells, NK cells may play a pathogenic role in RA, as reports have shown that the accumulation of NK cells in the inflammatory joints of individuals with RA promotes monocyte-derived TNF-α production after being activated by inflammatory factors such as IL-12, IL-15, and IL-18 [41]. Moreover, NK cells themselves express high levels of inflammatory mediators such as IL-1β, which accumulate in the synovium and promote inflammation, leading to joint and bone destruction [42]. Like NK cells, abnormal activation of innate lymphoid cells (ILCs) contributes to RA pathogenesis. ILCs exist mainly at the body's barrier surfaces, respond quickly to stress signals, and play key roles in tissue remodeling, pathogen resistance, and tissue homeostasis. Specifically, ILC3 $CCR6^{+}$ cells lead to RA inflammation via excessive IL-17 and IL-22 production [36], whereas the number of ILC2 cells is reduced in the synovium of RA patients, resulting in low regulatory T-cell (Treg) activity and decreased level of inflammation [43]. In addition, DCs, the key professional antigen-presenting cells that connect innate and adaptive immune responses [44], are not excluded from the pathogenesis and progression of RA [36]. In particular, monocyte-derived DCs, a subtype of DCs, are enriched in the RA synovium and enhance T helper (Th) 17 cell expansion and induce proinflammatory cytokine production, whereas conventional DCs significantly promote T-cell activation [45]. T cells subsequently regulate the process of RA at multiple levels. Under the stimulation of inflammatory cytokines such as TGF-β, interferon-gamma (IFN-γ), IL-2, IL-12 and IL-21, T cells differentiate into Th1 cells and Th17 cells and produce inflammatory molecules including

IL-2, IL-4 and IL-10, which aggravate the inflammatory response [46,47]. Moreover, activated T cells stimulate neoangiogenesis and lymphoid organogenesis and promote synoviocyte expansion as well as the development of bone-eroding osteoclasts in inflamed joints [48].

The immune cells mainly release pro-inflammatory cytokines and mediate both systemic and local inflammatory responses [49], while FLSs, osteoclasts and chondrocytes act as local effector and target cells in joints. FLSs are activated by pro-inflammatory cytokines, releasing factors such as MMPs, causing excessive proliferation and migration, and subsequently leads to chondrocytes dysfunction [50] and cartilage degradation [51]. Inflammatory cytokines also promote osteoclast differentiation, thereby exacerbating bone resorption and injury [52]. These cells mediate the occurrence and development of RA synergistically.

FLSs, resident cells of synovium, act as important effector cells in inflamed joints, and play a crucial role in the pathogenesis of RA. FLSs accept information from immune cells and then excessively proliferate and migrate, which leads to thickening and fibrosis of synovial tissue. Abnormal proliferation of synovium is accompanied by the formation of new blood vessels, accelerating the infiltration of inflammatory cells and the hypoxic microenvironment of synovial tissue, further promoting joint destruction [53]. Moreover, activated FLSs promote synovial joint inflammation via the release of the proinflammatory cytokines TNF-α and IL-1β, the production of receptor activator of nuclear kappa-B ligand (RANKL), and the secretion of matrix metalloproteinases (MMPs), followed by the induction of chondrocyte dysfunction and osteoclast proliferation, ultimately leading to cartilage and bone destruction [51].

Osteoclasts, the primary bone-resorption cells, are also a typical feature of RA. MMP-3, secreted from osteoclasts induced by TNF-α and IL-6, is involved in joint destruction, whereas cathepsin K, expressed in osteoclasts induced by RANKL, plays a critical role in osteoporosis, both of which contribute to RA development. In addition, TNF-α, IL-6 and RANKL promote the differentiation of osteoclast progenitors into mature multinucleated osteoclasts, causing excessive bone resorption activity and bone injury[52].

Furthermore, chondrocytes also participate in RA pathogenesis as both the effector and target cells. As the only cell type in cartilage, chondrocytes are responsible for producing and maintaining the cartilaginous matrix [54]. However, under the influence of immune cells and inflammatory mediators, especially in RA, the pro-inflammatory cytokines such as IL-6 and TNF-α induce dysfunction, diminished viability and inhibited proliferation of chondrocytes [55]. In addition, matrix synthesis of chondrocytes has been proven to be dramatically decreased, while the production of multiple tissue-degrading enzymes (including matrix metalloproteinase (MMP)-1, -3, -13) are significantly increased, leading to extracellular matrix degradation and facilitating joint damage of RA [50,56].

Various signaling pathways are involved in the progression of RA, especially in the process of cytokine release. The Toll-like receptor (TLR) family plays an instructive role in the progression of RA. Studies have shown that TLRs interact with adapter proteins and activate various transcription factors such as nuclear factor (NF)-κB and activating protein (AP)-1, triggering specific immune responses and the production of cytokines, resulting in the erosion of joints and cartilage [57,58]. Concurrently, mitogen-activated protein kinase

(MAPK), another downstream factor of TLRs, also contributes to RA pathogenesis that excessive activation of MAPKs is closely associated with the destruction of articular cartilage and the inflammatory proliferation of synovial tissues [59]. Released cytokines further activate the Janus kinase (JAK)/signal transducers and activators of transcription (STAT) pathway, leading to enhanced expression of MMPs and exacerbated inflammatory responses in synovial tissues [60]. The interplay of these signaling pathways collectively drives the pathological development of RA. Therefore, immunomodulation and suppression of inflammatory responses have been considered as potentially effective strategies for the prevention and control of RA.

3. Roles of whole grains in health improvement

3.1 Effect of diets rich in whole grains on RA management

Currently, common and widely recommended dietary patterns, including the Mediterranean diet (MedDiet), Dietary Approaches to Stop Hypertension diet (DASH Diet), the Mediterranean-DASH Intervention for Neurodegenerative Delay Diet (MIND Diet), the Ornish Diet, and the Zone Diet, share the same key components, including whole grains, fruits, vegetables, nuts, legumes, etc. [61,62]. The MedDiet, DASH diet, and MIND diet, in particular, have been shown to be beneficial for the control of various diseases, including RA, in clinical trials (Table 1) (Figure 1A).

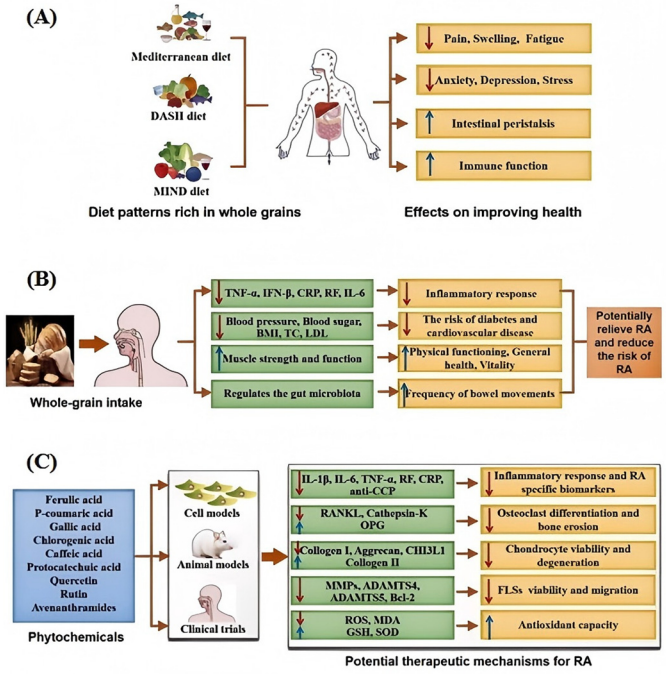

Figure 1. Overview of Multi-level Mechanisms of Whole Grain intake in RA management. (A) The potential health benefits of three different diet patterns rich in whole grains. (B) Potential mechanisms underlying the effects of whole grain intake on RA prevention and symptom improvement. (C) Potential mechanisms of phytochemicals abundant in whole grains in alleviating RA via suppressing inflammation and oxidative stress, and modulating the function of osteoclasts, chondrocytes, and FLSs.

DASH Diet: Dietary Approaches to Stop Hypertension diet; MIND Diet: Mediterranean-DASH Intervention for Neurodegenerative Delay Diet; TNF: tumor necrosis factor; IFN: interferon; CRP: C-reactive protein; RF: rheumatoid factor; IL: interleukin; BMI: body mass index; TC: total cholesterol; LDL: low-density lipoprotein; anti-CCP: anti-cyclic citrullinated peptide antibody; RANKL: receptor activator of nuclear factor-κB ligand; OPG: osteoprotegerin; Collagen I: type I collagen; CHI3L1: chitinase-3-like protein 1; Collagen II: type II collagen; MMPs: matrix metalloproteinases; ADAMTS: A disintegrin and metalloproteinase with thrombospondin motifs; Bcl: B-cell lymphoma; ROS: reactive oxygen species; MDA: malondialdehyde; GSH: glutathione; SOD: Superoxide Dismutase; RA: rheumatoid arthritis; FLSs: fibroblast-like synoviocytes.

Table 1. Clinical trials of dietary patterns with whole grains for the prevention and control of RA-related diseases.

Intervention Factors	Control	CTR number	Design	Enrolled Populations	Duration	Method	Result	Conclusion	Ref.
MedDiet	Noninter vention diet	NM	/	1183 adults aged 40–65	/	Questionnaires: CFQ, MFQ, SF-36, STAI-Y, PSS, CES-D, RSE-B, FFQ	Physical functioning, general health, vitality ↑ ; anxiety, depression, stress ↓	The MedDiet was associated with improved physical functioning and mental health.	64
MedDiet	Noninter vention diet	NM	Randomized, single-blind trial	180 patients with metabolic syndrome	2 years	Measurement indexes: inflammation markers, hs-CRP, endothelial function score, lipid and glucose parameters, insulin sensitivity	Endothelial function scores↑; body weight, hs-CRP, IL-6, IL-7, insulin resistance↓	The MedDiet may have been effective in reducing the prevalence of metabolic syndrome and its associated cardiovascular risk.	65
MedDiet	Low-fat diet	ACTRN1261 6000156482	Multicenter, parallel design, randomized controlled trial	65 patients (83% male) aged 53-71 with CHD	6 months	Measurement indexes: dietary compliance, anthropometry, body composition, venipuncture	Waist circumference and SAT area↓	The MedDiet reduced subcutaneous fat and waist circumference, improved obesity and reduced the risk of CHD.	66
MedDiet	Noninter vention diet	NCT044426 20	Randomized controlled trial	60 adults aged 40-60 years with NAFLD	6 months	Questionnaire: FFQ Measurement indexes: anthropometrics and clinical assessment, biochemical MedDiet parameters, hemogram, oxidative stress and inflammatory biomarkers	Cardiorespiratory fitness, catalase, SOD↑; weight, BMI, IFC, blood pressure, blood glucose, glycosylated hemoglobin, AST, ALT, GGT, CK-18, IL-6↓	Patients with NAFLD showed greater improvements in intrahepatic fat levels, cardiorespiratory health, and pro-oxidant and pro-inflammatory status.	69
MedDiet	Low-fat diet	NCT009249 37	Randomized, single blind, controlled trial	805 participants with T2D, prediabetes, and without T2D	3 years	Measurement indexes: FMD, endothelial function score	FMD, endothelial function↑	Long-term consumption of MedDiet improved endothelial function in patients with prediabetes and diabetes while preventing cardio-metabolic complications.	67
MedDiet	Low-fat diet	ACTRN1261 6000156482	Randomized controlled trial	56 patients (84% male) with CHD	6 months	Measurement indexes: DII	DII↓	The MedDiet intervention significantly reduced DII and thus the incidence of CHD.	68

MedDiet	Noninter vention diet	NCT017540 12	Parallel-group , multicentric, randomized, controlled clinical trial, *in vitro* experiment	272 participants aged 65-79 years	1 year	Measurement indexes: innate immune responses, circulating immune cells phenotype and the levels of proinflammatory, anti-inflammatory markers	IFN-β, $CD3^+CD28^+$ cells, $CD40^+CD86^+$ cells↑; IL-12Rβ1, IL-12p40/IL-12p70, SOCS3↓	The MedDiet influenced various parameters of immune function and improved immune function in older people.	[70]
MedDiet	Noninter vention diet	NM	/	327 adults in the Saudi region	/	Questionnaires: characteristics of general health, MedDiet compliance status, immune function	Immune status↑	The MedDiet was associated with immune status and treatment of chronic diseases.	[71]
MedDiet	Noninter vention diet	PACTR2020 0553885807 6	Double-blinde d, parallel groups, randomized, controlled clinical trial	60 women with RA	6 months	Measurement indexes: quadriceps and hamstrings muscles performance (agonist–antagonist ratio), VAS, CRP, handgrip strength, HAQ-DI, weight	Agonist–antagonist ratio↑; pain, CRP, HAQ-DI, fatigue from flexion, body weight↓	MedDiet should be considered as adjunctive therapy in treating females with RA.	[72]
MedDiet	Noninter vention diet	NM	/	1721 RA patients and 3667 healthy individuals	1 year	Questionnaire: FFQ Measurement indexes: RF, ACPA	RF, ACPA↓	MedDiet relieved the symptoms of RA and reduced the risk of RA in men.	[73]
MedDiet	Noninter vention diet	NM	Single center, randomized, parallel study	51 RA patients	3 months	Questionnaires: HAQ, SF-36 Measurement indexes: DAS-28, daily consumption of nonsteroidal anti-inflammatory drugs	Vitality↑; DAS28, HAQ, body weight, plasma cholesterol↓	The MedDiet was associated with reduced inflammatory activity, increased physical function, and improved vitality in RA patients.	[74]
DASH Diet	Noninter vention diet	NM	Multicenter cross-sectiona l study	100 RA patients and 200 healthy adults (93% female)	/	Questionnaires: DASH diet score, IPAQ Measurement indexes: nutrients intake, physical and biochemical indexes	There was a negative association between adherence to the DASH diet and RA in a sample of Iranian adults.	High adherence to DASH Diet may reduce risk of RA.	[76]
DASH Diet	Noninter vention diet	NM	Prospective cohort study	44,654 males	26 years	Questionnaires: medical history, current diet, lifestyle habits, FFQ, gout information questionnaire	Relative risk of morbidity decreased from 0.65 to 0.31.	High adherence to DASH Diet may reduce risk of gout.	[77]
DASH Diet	Noninter vention diet	NM	/	17,349 U.S. citizens aged ≥20 years (9.05% of them had OA)	/	Questionnaires: medical conditions questionnaire, DASH diet score. Measurement index:	There was a negative association between adherence to the DASH diet and OA, with each	High adherence to DASH Diet may reduce risk of OA.	[78]

						physical index	one-unit increase in DASH score being associated with a 3% reduction in the probability of developing OA.		
DASH Diet	Typical American Diet and FV Diet	NM	Three-arm, parallel-group, randomized controlled feeding trial	459 healthy individuals aged 22-75 years	8 weeks	Measurement indexes: physical index, blood pressure, lipids	Systolic blood pressure, TC↓	The DASH diet significantly reduced risk factors associated with ASCVD.	79
MIND Diet	Noninter vention diet	NM	Cross-sectional investigation	101 RA patients and 101 healthy individuals	/	Questionnaire: FFQ Measurement indexes: TCA, SOD, GPx, MDA, DAS-28, VAS, CRP	HDL-C↑; DAS-28, TG, LDL-C, TC, fasting blood glucose, hemoglobin A1C↓	Adherence to the MIND diet may reduce disease activity and the incidence of RA. High adherence to the MIND diet may improve lipid and glucose levels in RA patients.	81
MIND Diet	Low-calorie diet	IRCT20190427043387N1	Randomized controlled trial	37 healthy females age of (48 ± 5.38) years and a BMI of 32±0.69 kg/m^2	3 months	Questionnaire: FFQ Measurement indexes: blood sampling, clinical and anthropometric data, MRI	GLP-1, growth hormone-releasing peptide↑; weight, BMI, body fat percentage, waist circumference, leptin concentration↓	The MIND diet improved obesity.	82
MIND Diet	Noninter vention diet	NM	/	193 patients with stroke and 195 healthy individuals	/	Questionnaires: FFQ, MIND diet score, IPAQ, MET Measurement indexes: MRI, BMI	High adherence to the MIND diet was associated with a 59% reduction in the odds of stroke.	Adherence to the MIND diet reduced the risk of stroke.	83
MIND Diet	Noninter vention diet	NM	Case−control study	85 patients with AD, 170 healthy subjects	/	Questionnaires: FFQ, MIND diet score, GAD-7	There was a negative association between adherence to the MIND diet and AD.	Adherence to the MIND diet can alleviate AD symptoms and may reduce the risk of developing AD.	84

Notes: CTR: clinical trial registration; NM: not mentioned; MedDiet: mediterranean diet; CFQ: cognitive failure questionnaire; MFQ: memory functioning questionnaire; SF-36: 36-item short-form health survey; STAI-Y: state-trait anxiety inventory: form Y; PSS: perceived stress scale; CES-D: center for epidemiological studies-depression scale; RES-B: bachman revision of the rosenberg self-esteem scale; FFQ: food frequency questionnaire; T2D: type 2 diabetes; FMD: flow-mediated vasodilatation; hs-CRP: high-sensitivity C-reactive protein; IL: interleukin; NAFLD: nonalcoholic fatty liver disease; SOD: superoxide dismutase; BMI: body mass index; IFC: intrahepatic fat content; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl transferase; CK-18: cytokeratin 18; CHD: coronary heart disease; DII: dietary inflammatory index; SAT: subcutaneous adipose tissue; IFN: interferon; CD: cluster of differentiation; SOCS: suppressor of cytokine signaling; HAQ-DI: health assessment questionnaire-disability index; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibodies; VAS: visual analog scale.

The MedDiet is one of the most studied and well-known dietary patterns in the world [63], and the results of clinical trials have shown that the MedDiet markedly promotes physical functioning and vitality and reduces anxiety, depression, and stress [64]. In addition, people in the MedDiet groups presented decreases in insulin resistance, body weight, body mass index, blood pressure, blood glucose, glycosylated hemoglobin, and markers of liver injury[65-67], indicating the potential role of the MedDiet in health improvement. Further studies revealed that the changes in the levels of inflammation-related markers including C-reactive protein (CRP), IL-6, and IL-7 in people in intervention groups consuming a MedDiet dramatically decreased in comparison with those in people in low-fat diet or nonintervention diet groups [65,68,69], and there was also a positive association between the MedDiet intake and improved immune function [70,71]. In particular, the MedDiet not only significantly downregulated rheumatoid factor (RF), anti-citrullinated protein antibodies, and the Health Assessment Questionnaire (HAQ) scores, but also alleviated pain, fatigue, and weight loss compared with the nonintervention diet in patients with RA [72-74], indicating the benefits of MedDiet for inflammation reduction and RA management.

The DASH diet, which is recommended by the International Diabetes and Heart Association guidelines, mainly includes whole grains, fruits, and vegetables but limits food with high salt, high sugar and saturated fat contents [75]. Like the MedDiet, population trials conducted on the DASH diet also revealed reduced risks of RA, osteoarthritis (OA) and gouty conditions [76-78], as well as atherosclerotic cardiovascular disease [79].

The MIND diet, a hybrid of the MedDiet and the DASH diet, focuses on natural plant foods such as fruits and vegetables, whole grains, legumes and olive oil while limiting the intake of animal foods and high saturated fat [80]. With the intervention of the MIND diet, the blood lipid and blood glucose levels of patients are well controlled, and the disease activity and incidence of RA dramatically decrease [81]. In addition, the MIND diet helps reduce the risk of chronic diseases such as stroke and obesity, which also contributes to mental health and neuroprotection, as well as potential benefits for RA prevention [82-84]. These findings highlight the value of a diet enriched with whole grains for RA prevention and treatment.

3.2 Potential roles of whole grain intake in RA management

There is a wealth of evidence that whole grains are more effective than refined grains in promoting health and preventing chronic diseases, especially inflammation-related diseases (Table 2) (Figure 1B). Several population-based trials have shown that whole grains not only decreased the body mass index (BMI), waist circumference [85], total cholesterol (TC), low-density lipoprotein (LDL), and fasting blood glucose, but also acted as experts in enhancing intestinal peristalsis and optimizing the intestinal microbiota (specifically increasing the relative abundance of *Ackermannia* and *Lactobacillus*) [86]. These changes are beneficial for delaying the development of chronic diseases such as cardiovascular disease, obesity, and diabetes [87,88]. Furthermore, the intake of whole grains 50 g/1000 kcal daily has also been reported to alleviate the symptoms of skeletal muscle atrophy by improving protein turnover, stimulating of net muscle protein synthesis, and enhancing muscle function [89]. Since both obesity and hyperlipidemia are considered as risk factors for RA, and loss of muscle mass and strength is common in patients with RA [90], whole grains may indirectly contribute to the prevention and treatment of RA.

Table 2. Clinical trials of whole grain supplementation for the prevention of RA-related diseases.

Whole Grain Interventions	Control	CTR number	Design	Subjects	Duration	Method	Result (WG group)	Conclusion	Ref.
WG	RG	NM	/	5094 subjects with a mean age of 56 years	/	Questionnaire: FFQ Measurement indexes: BMI, waist circumference, diastolic and systolic blood pressure, HDL-C, LDL-C, TG, CRP, glucose	Nutrition quality (both sexes)↑; BMI, waist circumference, TC (male)↓	WG intake was associated with small improvements in the chronic disease risk factors in men.	85
WG	RG	NCT01403857	Intervention trial	46 healthy subjects aged 19 to 46 years	6 weeks	Measurement indexes, body composition, fecal microbiota, fasting blood glucose, TC, HDL, LDL, triglycerides	Frequency of bowel movements, abundance of *Akkermansia* and *Lactobacillus*↑; TC, LDL, non-HDL-C, fasting blood glucose↓	Increasing the consumption of WG may significantly lower fasting measures of TC, LDL, and non-HDL cholesterol.	86
WG wheat	Refined wheat	NM	Open-label parallel intervention	79 postmenopausal females aged 45-70 years with BMI 27-37 kg/m^2	12 weeks	Measurement indexes: body weight and composition, blood pressure, concentration of circulating risk markers	Fat mass percentage, BMI, waist circumference, TC, LDL-C↓	WG had cardioprotective properties.	87
WG	RG	ISRCTN27657880	Randomized, single-blind, controlled, parallel-designed trial	206 subjects aged 40-65 years	12 weeks	Measurement indexes: weight, health status, level of exercise, medication use, TC, LDL-C, insulin sensitivity, inflammation, BP	SBP, PP↓	Daily consumption of 3 portions of WG foods can significantly reduce the risk of cardiovascular disease in middle-aged populations.	88
WG	RG	NCT01411540	Double-blind, crossover, randomized controlled trial	14 subjects aged 20-50 years with a BMI of 25-38 kg/m^2 and low daily intake of WG	8 weeks	Measurement indexes: cardiovascular, glucose metabolism, protein metabolism outcomes	WBPT, 24-h integrated net protein balance, muscle function↑; weight↓	WG components augment global protein synthesis in skeletal muscle, and that greater whole-grain intake might preserve muscle function in older adults.	89
WG	Refined grains, FV	NCT02602496	Randomized, parallel arm feeding trial	49 subjects with overweight or obesity and low intakes of FV and WG	6 months	Measurement indexes: Inflammatory markers: TNF-α, IL-6, LBP, hs-CRP; stool sample: S/BCFA, microbiota composition	LBP, TNF-α↓	WG intake regulated the gut microbiota, reduced inflammation and the risk of metabolic syndrome.	91
WG wheat	Refined wheat	NCT012931	Placebo-controll	80 subjects with	8 weeks	Measurement indexes: blood,	IL-10, DHFA, FA↑;	WG intake promoted a	92

		75	ed, parallel-group randomized trial	overweight or obesity and low intakes of FV		urine, feces, anthropometric and body composition	TNF-α, IL-6, plasma plasminogen activator inhibitor 1↓	positive immune response, which reduced the risk of obesity-related diseases.	
WG	RG	NCT01731366	Randomized, controlled crossover trial	50 subjects aged 20-64 with metabolic syndrome	8 weeks	Measurement indexes: gut microbiome composition, insulin sensitivity, glucose and lipid metabolism, gut functionality, inflammatory markers, anthropometry, urine metabolomics	Weight, serum inflammatory markers, IL-6, CRP↓	WG intake did not alter insulin sensitivity and gut microbiome but reduced body weight and systemic low-grade inflammation.	94
WG	/	IRB Approval Number: 5298	Randomized crossover trial	28 healthy adults	4 weeks	Measurement indexes: fecal microbial ecology and blood markers of inflammation, glucose and lipid metabolism	IL-6, hs-CRP, peak postprandial glucose, fasting blood glucose, total cholesterol↓	Short-term WG intake changed gut microbiota and improved metabolic functions.	93
WG	RG	NCT01902394	Randomized, controlled, parallel-design human trial	49 males and 32 postmenopausal females aged 40-65	6 weeks	Measurement indexes: stool, 12-h fasting blood, saliva samples, DTH skin-tests, immune and inflammatory responses, gut microbiota, microbial products	Fecal volume and frequency of bowel movements, stool acetate, total SCFAs, effector memory T-cell↑; proinflammatory *Enterobacteriaceae*↓	Short-term WG intake improved inflammation.	95

Notes: CTR: clinical trial registration; WG: whole grain; RG: refined grain; NM: not mentioned; FFQ: food frequency questionnaire; BMI: body mass index; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TG: triglycerides; hs-CRP: high-sensitivity C-reactive protein; TC: total cholesterol; SBP: systolic blood pressure; PP: pulse pressure; WBPT: whole-body protein turnover; FV: fruits and vegetables; TNF: tumor necrosis factor; IL: interleukin; LBP: lipopolysaccharide binding protein; S/BCFAs: short/branched chain fatty acids; DHFA: dihydroferulic acid; FA: ferulic acid; DTH: delayed-type hypersensitivity.

Moreover, whole grains have a positive impact on inflammation and immunity. Specifically, whole-grain intervention has been shown to decrease inflammatory responses by reducing the production of lipopolysaccharide (LPS)-binding proteins and proinflammatory cytokines and lowering the risk of metabolic syndrome compared with refined grains [91]. In a trial of obese or overweight populations, whole-grain intervention significantly decreased the levels of TNF-α and IL-6, but increased IL-10 expression compared with those of refined-grain intervention [91]. Furthermore, the results of several population-based trials revealed reduced CRP levels with whole-grain supplementation [93,94], indicating the potential role of whole-grain intervention in the anti-inflammatory process. In addition, whole grains have been shown to enhance effector memory T cells and acute innate immune responses [95], indicating their ability to modulate immunity. Since RA is considered a chronic autoimmune disease that characterized by joint inflammation, we speculate that whole-grain supplementation potentially contributes to the inhibition of RA, and more in-depth research is still needed to confirm this.

4. Potential roles of whole-grain ingredients in RA

Compared with refined grains, whole grains possess health-promoting bioactive components in their bran and germ, offering more complex and beneficial nutritional profiles. In particular, phytochemicals, such as phenolic acids, flavonoids and avenanthramides (Avns), as well as nutrients, including DF, vitamins and minerals may play important roles in the treatment of RA. Studies have shown that the bioactive components in whole grains primarily improve RA by modulating FLSs, osteoclasts, and chondrocytes (Figure 2).

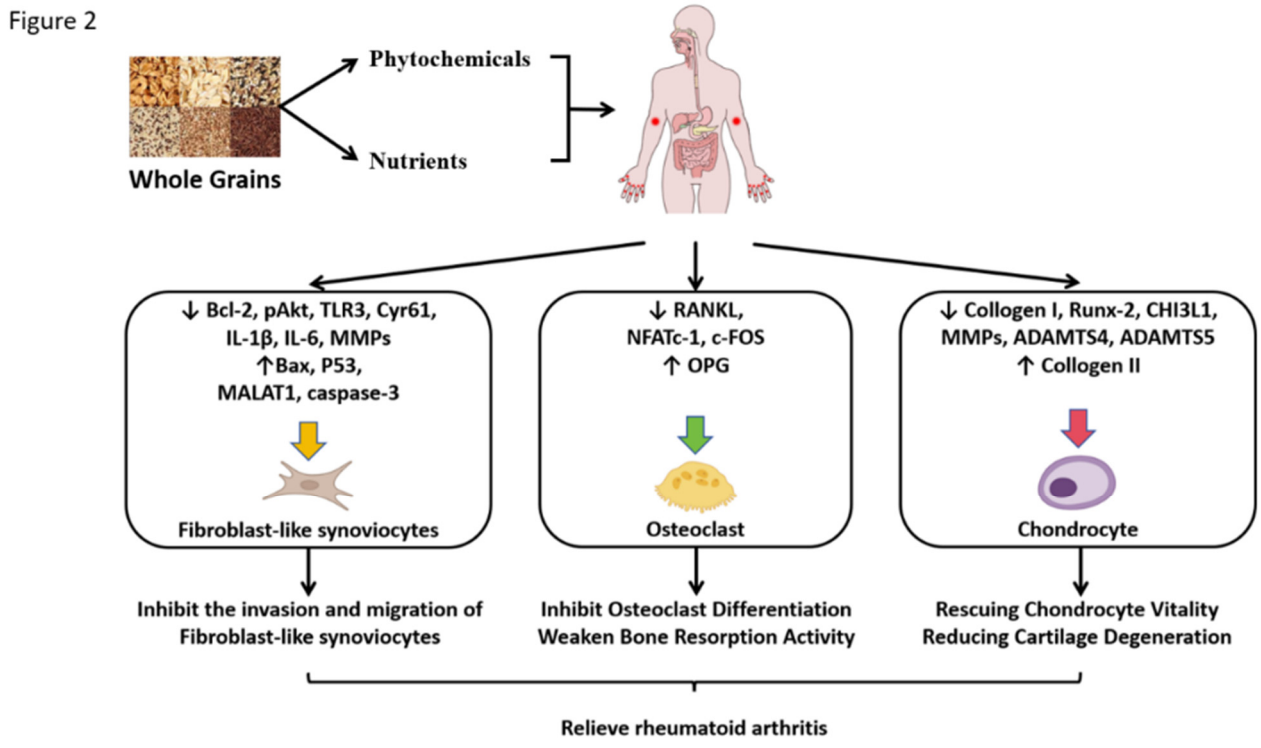

Figure 2. The main potential mechanisms by which whole grains alleviate local tissue symptoms of RA.

Whole grains can reduce the invasion and migration of synovial fibroblasts by inhibiting the expression of cellular inflammatory factors and signaling pathways. They also suppress osteoclast differentiation, decrease bone resorption activity, preserve chondrocyte viability, and mitigate cartilage degeneration.

Bcl: B-cell lymphoma; pAkt: phospho-Akt; TLR3: toll-like receptor 3; Cyr: cysteine-rich angiogenic inducer; IL: interleukin; MMPs: matrix metalloproteinases; Bax: Bcl-2-associated X protein; P53: tumor protein p53; MALAT1: metastasis-associated lung adenocarcinoma transcript 1; Caspase-3: cysteine-aspartic acid protease 3; RANKL: receptor activator of nuclear factor kappa-B ligand; NFATc-1: nuclear factor of activated T cells cytoplasmic 1; OPG: Osteoprotegerin; Collagen I: type I collagen; Collagen II: type II collagen; Runx-2: runt-related transcription factor 2; CHI3L1: chitinase-3-like protein 1; ADAMTS: A disintegrin and metalloproteinase with thrombospondin motifs.

4.1 Effects of phytochemicals in whole grains on RA management

Whole grains are rich in phytochemicals, including phenolic acids, flavonoids, etc.[20,96]. Taking whole meal flour as an example, the bran/germ fraction contributes 83% of the total phenolic content and 79% of the total flavonoid content [20]. *In vivo* and *in vitro* studies as well as clinical trials have demonstrated that these substances serve as important factors in the anti-inflammatory activity of whole grains and even contribute to the inhibition of RA [97]. Details of the relevant human and animal experiments related to phytochemicals are provided in Figure 1C and Table 3. Therefore, the next part of this paper describes the progress of research on the inhibition of RA by each of these components.

Table 3. Suppression of rheumatoid arthritis by phytochemicals in whole grain.

Phytochemicals Name	Dose/Duration	Animal Model/Cell line	Mechanism	Ref.
Ferulic Acid	25, 50, 100 mg/kg/21 days	rat/ CFA	TGF-β↑; CRP, RF, TNF-α, JAK2↓	106
Ferulic acid ethyl esther	12.5, 25, 50, 100 mg/kg/ 14 days	rat/ CFA	TNF-α, IL-1β↓	107
Ferulic Acid	5, 10, 20 μM/ 24 h	LPS-activated THP-1 macrophages	TNF-α, IL-1β, IL-6, NLRP3↓	108
Ferulic Acid	125, 250, 500 μM/ 24 h	LPS-activated THP-1 macrophages	NF-κB, TNF-α, IL-1β↓	109
Ferulic Acid	25, 50, 100 μM/ 24 h	rat/ RAW 264.7 monocyte/macrophages	NF-κB, NFATC1, c-Fos, MMP-9, Cathepsin K↓	110
Ferulic Acid	25, 50,100 μM/ 24 h	rat/ AIA	OPG↑; IL-17/IL-17RA/STAT-3, TLR-3, Cyr61, IL,23, GM-CSF, RANKL↓	111
Ferulic Acid	5, 10 μmol/L/ 24 h	Human/ chondrocyte	IL-6, PGE2, nitrite, Collagen I, Runx-2, MMP-1, MMP-3, MMP-13↓	112
Ferulic Acid protocatechuic acid caffeic acid	0.1 mM/ 20 min	Human/neutrophils	ROS↓	114
p-coumaric acid	100 mg/kg/ 16 days	rat/ AIA	TNF-α, IL-1β, IL-6, IL-17, MCP-1, iNOS, COX-2, NFATC1, c-Fos, RANKL↓	117
p-coumaric acid	30 mg/kg/ 9 days	rat/ AIA	TNF-α, IL-1β, IL-6, IL-23, iNOS, COX-2, MMP-9, NFATc1↓	118
p-coumaric acid	100 mg/kg/ 21 days	rat/ AIA	TNF-α, macrophage phagocytic index↓	119
p-coumaric acid	100 mg/kg/ 8 days	rat/ AIA	Leukocytes infiltration↓	120
p-coumaric acid	10, 20, 40 μg/ml/ 24 h	rat/ OA	MAPK, NF-κB, COX-2, iNOS, MMP-1, MMP-3, MMP-13, ADAMTS4, ADAMTS5↓	121
Gallic Acid	20,40,80 mg/kg/ 22 days	rat/ CIA	IL-10, TGF-β↑; MMP-3, MMP-9, MMP13, IL-17, IL-6, IFN-γ, TNF-α↓	129
Gallic Acid	6.25, 12.5, 25 and 37.5 μg/ml/ 24 h	rat/ Macrophages	M1 macrophage polarization, iNOS, TNF-α, IL-1β, COX-2, p-STAT1↓	131
Gallic Acid	0.1, 0.25, 0.5, 1, 2, 5,10 mmol/l/ 6 h; 1,5,10 μg/g/ 24 h	minipig/ neutrophils rat/ CFA	IL-6↑; TNF-α, PDE4↓	132
Gallic Acid	0.1, 1, 10, 50, 100 μmol/L/ 48 h	human/ FLS	p53, Bax↑; Bcl-2, pAKT, IL-1β, IL-6, CCL-2/MCP-1, CCL-7/MCP-3, COX-2, MMP-9↓	133
chlorogenic acid	30, 60 mg/kg/ 26 days	rat/ CIA	TNF-α, BAFF↓	139
chlorogenic acid	/	rat/ CIA and human/ FLS	JAK2, STAT3, TNF-α, IL-6, IL-17, IL-23↓	140
chlorogenic acid	2, 5, 20 μmol/L/ 24 h	RAW 264.7 and BV2 macrophage cells	NF-κB, TNF-α, IL-1β, IL-6, NO, COX-2. iNOS↓	141
chlorogenic acid	2.5, 5, 10, 20 and 40 mg/kg/ 13 days	rat/ AIA	Th2 cytokines↑ ; TNF-α, IL-1β, Th1 cytokines↓	142
chlorogenic acid	5, 10, 25, 50 and 100 μmol/L/ 24 h	rat/ FLS	JAK/STAT, NF-κB, IL-6↓	144
chlorogenic acid	5, 10, 25, 50 and 100 mmol/L/ 24 h	rat/ FLS	JAK/STAT, NF-κB, IL-1β↓	143
Eucommia Chlorogenic	25, 50, and 100 mg/kg/ 28 days	rat/ CFA	TNF-α, IL-1β, IL-6, IL-17, COX-2↓	145

Acid				
Zinc Oxide Nanoparticles (including Caffeic acid and Rosmerinic acid	2 mg/kg b.wt./day/ 20 days	rat/ CIA	NF-κB, TNF-α, IL-1β, IL-6, COX-2↓	149
Caffeic acid	50 mg/kg/ 20 days	rat/ AIA	GSH↑; NF-κB, CHI3L1, IL-1β, MMP-9, MDA, NO↓	150
Caffeic acid	1, 10, 20, 30 μmol/L/ 24 h	human/ FLS	IκBα, IKKα/β, NF-κB, IL-6, TNF-α, PGE2, MMP-1↓	152
n-butanol fraction of Trianthema portulacastrum (rich in Protocatechuic acid)	100, 200, 400 mg/kg for 21 days	rat/ CFA	IL-1β, IL-6, IL-7, IL-23, TNF-α↓	157
Protocatechuic acid	5, 10, 20, 40 μmol/L/ 48 h	human/ FLS	NF-κB, Akt/mTOR, TNF-α, IL-1β, IL-6, MMP-3, MMP-13↓	158
Protocatechuic acid	10, 20,40 μmol/L/ 48 h	human/ FLS	Nrf2/Keap1↓	160
Quercetin	500 mg/ 8 weeks	Human/ RA	EMS, TNF-α, HAQ, Morning pain and after-activity pain↓	170
Quercetin	200 μl of 100 mg/kg/ three times per week for 3 weeks	rat/ CFA	IL-1β, IL-6, TNF-α, ADA↓	171
Quercetin	150 mg/kg·0.5 mL/ three times per week either from day 21 or day 28 until the termination of the experiments.	rat/ CIA	TNF-α↓	172
Quercetin	0.5%/ 9 weeks	rat/ CIA	TNF-α, IL-1β, MCP-1, NO, PGE2↓	174
Quercetin	50 nmol/l/ 2 h	human/ FLS	IL-1β, IL-6, IL-8, XIST↓	177
Quercetin	10, 20, 30 μmol/L/ 48 h	human/ FLS	miR146a↑; GATA6↓	178
Quercetin	10, 50, 100, 150, 200, 300 μmol/L/ 72 h	human/ FLS	lncRNA MALAT1↑; PI3K/Akt↓	179
Quercetin	100, 200, 300 μmol/L/ 48 h	human/ FLS	Bcl-2/Bax↓	180
Quercetin	1, 5, 25 μmol/L/ 3 h	human/ FLS	Th17, IL-17, RANKL↓	182
Rutin	25, 50 mg/Kg/ 22 days	rat/ CIA	NF-κB, iNOS↓	187
Rutin	10 μg/ml/ 24 h	rat/ chondrocytes	NF-κB, MAPK, SIRT1, TNF-α, IL-1β, MMP-2, MMP-9, COX-2, iNOS↓	188
Rutin	0.1, 1, 10, 50, 100 μmol/L/ 24 h	rat/ RAW 264.7 Macrophages	TNF-α, IL-6, NO, PGE2↓	189
Rutin	5, 10, 15 mg/Kg/ 28 days	rat/ CFA	SOD, GPx, GSH↑; NF-κB p65, TNF-α, IL-1β, MDA↓	190

Notes: RA: rheumatoid arthritis; OA: osteoarthritis; CFA: complete Freund's adjuvant; LPS: lipopolysaccharide; AIA: adjuvant-induced arthritis; CIA: collagen-induced arthritis; FLS: fibroblast-like synoviocytes; JAK: janus kinase; TNF: tumor necrosis factor; IL: interleukin; TGF: transforming growth factor; CRP: C-reactive protein; RF: rheumatoid factor; NLRP3: NOD-like receptor protein 3; NF-κB: nuclear factor-κB; NFATC1: nuclear factor of activated T cells cytoplasmic 1; MMPs: matrix metalloproteinases; STAT: signal transducers and activators of transcription; TLRs: toll-like receptors; Cyr: cysteine-rich angiogenic inducer; GM-CSF: granulocyte-macrophage colony-stimulating factor; RANKL: receptor activator of nuclear kappa-B ligand; OPG: osteoprotegerin; PGE2: prostaglandin E2; Runx-2: runt-related transcription factor 2; ROS: reactive oxygen species; MCP: monocyte chemoattractant protein; iNOS: inducible nitric oxide synthase; MDA: malondialdehyde; COX: cyclooxygenase; GPx: glutathione peroxidase; MAPK: mitogen-activated protein kinase; ADAMTS: a disintegrin and metalloproteinase with thrombospondin motifs; HAQ: health assessment questionnaire; PDE: phosphodiesterase; Bcl: B-cell lymphoma; pAkt: phospho-Akt; BAFF: B-cell activating factor; Th: T helper cell; CHI3L1: chitinase-3-like protein-1; NO: Nitric oxide; GSH: Glutathione; IKK: IκB kinase; EMS: early morning stiffness; ADA: adenosine

deaminase; XIST: X-inactive specific transcript; GATA: GATA transcription factor; MALAT1: metastasis-associated lung adenocarcinoma transcript 1; SIRT: silent information regulator.

4.1.1 Phenolic acids

Whole grains are a significant source of phenolic acids, including FA, PCA, gallic acid (GA), chlorogenic acid (CGA), caffeic acid (CA), and protocatechuic acid (PRA) (Figure 3), which are present mainly in the aleurone layer, bran, and germs of nearly all whole grains [98]. Among these, FA is the most common phenolic acid in whole grains and is found primarily in the bran, aleurone layer, pericarp, and cell walls of the embryo. The FA content is greater in wheat, oats, and rice than in other phenolic acids, with specific levels reported as (333.44 ± 16.20) μmol/100 g in wheat, (184.66 ± 4.61) μmol/100 g in oats, and (153.39 ± 8.68) μmol/100 g in rice, while corn shows the highest concentration at (906.13 ± 9.09) μmol/100 g [99], whereas CGA is widely present in buckwheat whole grains [100]. These phenolic acids possess antioxidant properties due to their aromatic phenol rings and have potential anticancer, anti-inflammatory, and antimicrobial effects [98,101,102]. Both preclinical and clinical studies indicate that phenolic acids play critical roles in preventing and relieving RA.

Figure 3

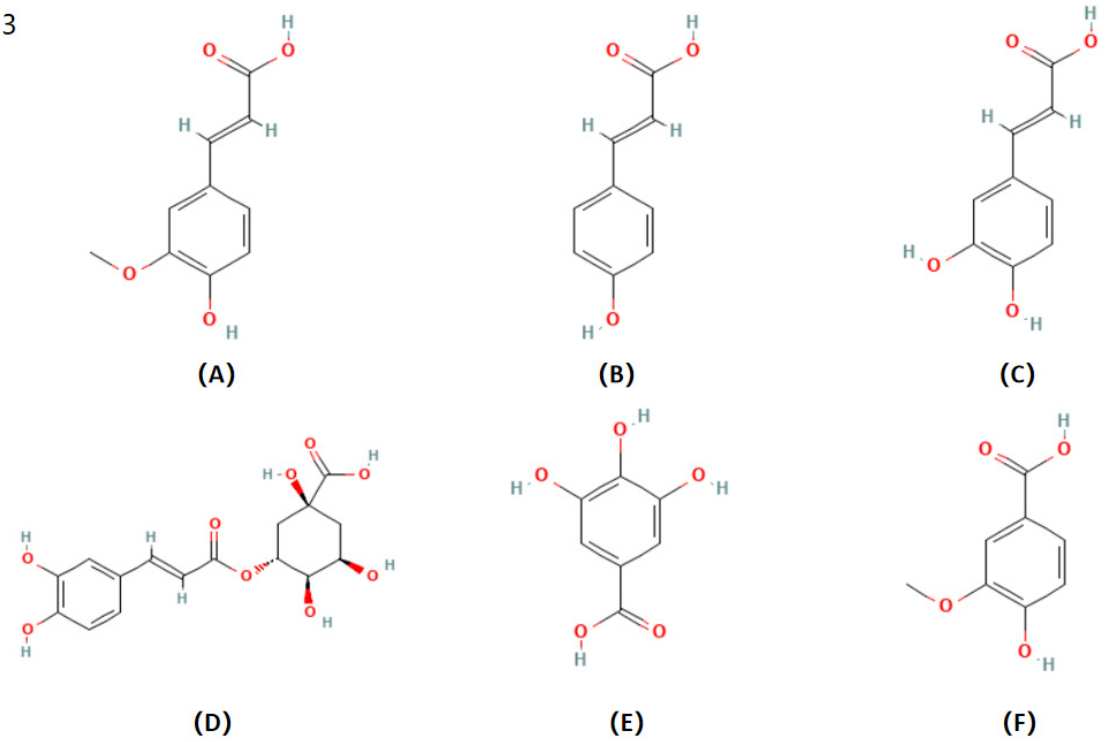

Figure 3. The chemical structures of the six phenolic acids that improved the effects of RA.
(A) Ferulic acid; (B) p-coumaric acid; (C) caffeic acid; (D) chlorogenic acid; (E) gallic acid; (F) protocatechuic acid.

4.1.1.1 Ferulic acid.

FA is the most abundant phenolic acid in common grains, accounting for 90% of the total phenolic compounds [103]. Owing to the hydroxyl and methoxy groups attached to the benzene ring, it exhibits significant antioxidant activity [104]. Currently, FA is used for the prevention and treatment of diseases caused by oxidative stress, including Alzheimer's disease, diabetes, cancer, hypertension, and atherosclerosis [105].

Additionally, FA possesses a strong ultraviolet absorption capacity, making it a promising photoprotective agent [103].

Recent studies indicate that FA has potential for the treatment of RA. Treatment with FA (25 mg/kg, 50 mg/kg, or 100 mg/kg) significantly relieved RA by inhibiting paw edema, reducing the arthritic score, and reversing changes in biochemical parameters and inflammatory markers such as CRP and RF in complete Freund's adjuvant (CFA)-induced arthritis model rats [106]. Ferulic acid ethyl ester, a derivative of FA, also showed remarkable antiedema effects that it reduced joint swelling and improved disability in CFA-induced arthritis rats [107]. Further research confirmed that FA reduced macrophage activity and inhibited the phosphorylation of NF-κB and the activation of the NOD-like receptor family pyrin domain-containing 3 inflammasome in macrophages in a dose-dependent manner, thereby attenuating the secretion of inflammatory cytokines, including TNF-α, IL-6, and IL-1β, and resulting in a suppressed inflammatory reaction [108,109]. This anti-inflammatory effect at least partially contributed to the inhibition of osteoclast maturation and chondrocyte degeneration, which was beneficial for relieving local symptoms of RA, such as edema and joint swelling. Furthermore, FA acts directly on osteoclasts, chondrocytes and FLSs to inhibit bone erosion and pathological changes in cartilage tissue. In an *in vitro* study with RAW 264.7 monocytes, FA dramatically suppressed RANKL-induced osteoclast differentiation and bone resorption activity, suggesting the essential role of FA in bone erosion [110]. In addition, The expression of TLR-3, cysteine-rich angiogenic inducer 61, IL-23, and GM-CSF was downregulated by FA via the inhibition of the STAT-3 signaling cascade in FLSs isolated from adjuvant-induced arthritis rats, and FA exhibited significant ligand efficiency toward IL-17 RA, STAT-3, and IL-23 [111]. Moreover, FA has been shown to activate the silent information regulator 1 (SIRT1)/AMP-activated protein kinase (AMPK)/peroxisome proliferator activated receptor γ coactivator-1α (PGC-1α) signaling pathway, inhibiting the production of prostaglandin E2 (PGE2), nitrite, IL-6, and MMPs and dose-dependently rescuing chondrocyte viability. FA also counteracted IL-1β-induced chondrocyte degeneration by inhibiting the expression of the chondrocyte differentiation markers type I collagen and Runt-Related Transcription Factor 2 and restoring the expression of type II collagen and aggrecan [112]. Neutrophil infiltration into synovial joints has been considered as a hallmark of RA [113] that could resulted in the production of active oxygen by NADPH oxidase in intracellular structures with phorbol myristate acetate stimulation. FA significantly captured and eliminated the active oxygen produced by phorbol myristate acetate-stimulated neutrophils, both intracellularly and extracellularly, and at least partially inhibited NADPH oxidase activity, indicating the potential role of neutrophils in attenuating RA with FA administration [114].

4.1.1.2 P-Coumaric acid.

P-coumaric acid (PCA) is a phenolic acid synthesized in plants via the shikimate pathway, in which phenylalanine and tyrosine are used as precursors. PCA also serves as a precursor for other phenolic compounds, such as CA, FA, CGA, and sinapic acid [115]. PCA is widely distributed in both free and

conjugated forms in fruits, vegetables, and grains, with the content high in the bran of barley, wheat, oats, and corn among whole grains [116]. PCA has strong anti-inflammatory and antioxidant properties, primarily attributed to the structure of its hydroxyl and carboxyl groups, and has been found to alleviate atherosclerosis and has antimutagenic, antulcer, antiplatelet, antianxiety, antigout, and anticancer effects [115].

Like FA, PCA intervention also had a significant inhibitory effect on RA. Studies on adjuvant-induced arthritis (AIA) rats demonstrated that PCA significantly attenuated paw edema and weight loss by suppressing bone destruction and degrading cartilage [117]. Further research has explored the mechanism by which PCA treatment inhibits the expression of the inflammatory mediators TNF-α, IL-1β, IL-6, and IL-23, as well as circulating immune complexes, thereby reducing rat-mediated immune responses and macrophage phagocytic activity, resulting in suppressed systemic inflammatory reactions in AIA rat models [118,119]. Furthermore, PCA inhibits osteoclastogenesis and reduces the risk of joint deformities [117]. Moreover, polymorphonuclear leukocytes infiltrate joints and release PGE2, which enhances exudative responses and mediates further infiltration and swelling through its potent vasodilatory effect [120]. In an *in vivo* study on AIA rats, PCA inhibited LPS-induced PGE2 synthesis, resulting in reduced leukocyte infiltration and relieved paw edema in arthritic rats [120]. In addition, PCA has been shown to mitigate IL-1β-induced cartilage matrix degradation in rats by modulating the expression of inflammatory molecules and degradative enzymes, including inducible nitric oxide synthase (iNOS), cyclooxygenase (COX)-2, MMP-1, MMP-3, and MMP-13, as well as a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) 4 and ADAMTS 5, via the inhibition of the MAPK and NF-κB signaling pathways, thereby alleviating cartilage degeneration, which may also be beneficial for RA management [117,121].

4.1.1.3 Gallic acid.

Gallic acid (GA), an organic acid with a single benzene ring structure [122] characterized by three adjacent -OH groups at positions 3, 4, and 5 and a -COOH group at position 1 on the benzene ring, is widely present in the roots, stems, leaves, fruits, bark, flowers, and seeds of various plants [123]. It is also distributed in the bran of whole grains such as oats [124], sorghum [125], rice [21], and wheat [126]. GA has been shown to have remarkable antioxidant properties, as well as anti-inflammatory, antibacterial, and anticancer effects [127]. In particular, GA is the precursor of the antibacterial drug trimethoprim [128].

The administration of GA at doses of 40 and 80 mg/kg has been shown to significantly reduce the clinical arthritis score and hind paw volume in collagen-induced arthritis (CIA) model mice, indicating that GA has the potential to be a new therapeutic approach for RA [129]. Like FA, GA influences macrophages, thereby improving the body's immune response. GA reduces the levels of the cellular inflammatory factors TNF-α, IL-1β, and IL-6, preventing inflammatory damage in LPS-induced rat macrophages through the TLR4/NF-κB pathway, and thereby mitigating the degradation of glycoproteins and the release of collagenase, which contributes to bone and cartilage damage [130]. GA also significantly inhibited M1 macrophage polarization through the AMPK signaling pathway, preventing macrophage polarization toward

an anti-inflammatory phenotype [131]. Additionally, studies have indicated that GA affects neutrophils and T cells. GA not only inhibited cAMP-phosphodiesterase 4 activity in neutrophils, reduced TNF-α expression, and increased the levels of IL-6 and cAMP [132], but also alleviated the imbalance between Th17 and Treg cells in a CIA mouse model [129]. GA further acts on FLSs that GA effectively reduced FLS viability and even induced cell apoptosis in a study of FLSs isolated from RA patients [133] indicating the role of GA on RA.

4.1.1.4 Chlorogenic acid.

Chlorogenic acid (CGA), another class of abundant plant polyphenols, is an ester formed from CA and quinic acid and is widely distributed in herbs, fruits, and vegetables [134]. Moreover, CGA is a crucial phenolic acid component in certain whole grains, including oats [135], barley [136], wheat [137], and sorghum [138]. Recent studies have indicated that CGA possesses various biological properties, including antioxidant, antihypertensive, antimicrobial, antitumor, anti-inflammatory, and anti-HIV-1 activities, and has attracted considerable attention [137].

CGA significantly decreased paw thickness, swelling, and bone erosion and reduced the arthritis index in a dose-dependent manner by inhibiting the STAT3 and JAK2 signaling pathways in CIA rats [139,140]. Similar to that of GA, the alleviation of RA by CGA may also be related to its ability to suppress macrophage activity and modulate the activity of macrophages [141]. In addition, CGAs are involved in the immune system and act as effective T-cell response modulators. The results showed that CGA significantly inhibited the secretion of Th1 cytokines while increasing the production of Th2 cytokines and even suppressed delayed-type hypersensitivity [142], which might also be beneficial for preventing RA. Like other phenolic acids, CGA and its derivatives inhibited the expression of cytokines such as TNF-α, IL-1β, and IL-6 at both the mRNA and protein levels through the JAK/STAT and NF-κB signaling pathways [143,144]. In addition, CGA inhibits ROS production, thereby exerting anti-inflammatory and antioxidant effects. Moreover, both *in vivo* and *in vitro* studies revealed that the proliferation of FLSs was significantly inhibited by CGA intervention via the promotion of autophagy and induction of cell apoptosis, indicating that CGA is involved in regulating RA [143-145].

4.1.1.5 Caffeic acid.

Caffeic acid (CA) is a major phenolic acid in foods and is commonly found in both free and esterified forms[146]. CA has a wide range of sources, including olive oil, white wine, spices, potatoes, coffee beans, apples, plums, cranberries, and almost all whole grains [146,147]. CA has been shown to possess anti-inflammatory, antitumor, and immunomodulatory properties, contributing to the improvement of various diseases [148].

Nanoparticles containing CA and rosmarinic acid reduce biomarkers such as RF, anti-cyclic citrullinated peptide antibody, and CRP and relieve paw edema in CIA rats [149]. Studies on AIA rats have shown similar results: chitinase-3-like protein 1, a histological marker for the immunopathological diagnosis of RA, was dramatically downregulated with CA treatment [150,151]. Moreover, the NF-κB signaling pathway

and its downstream effectors such as TNF-α and MMP-9 were also inhibited, leading to minimal joint damage, cartilage degeneration, and bone erosion [149,150]. Furthermore, a study focusing on FLSs indicated that CA attenuated the inflammatory response in FLSs induced by IL-1β via inhibiting IκB kinase (IKK) α/β and IκBα phosphorylation [152]. Additionally, CA increases glutathione (GSH) levels and decreases malondialdehyde (MDA), NADPH, and nitric oxide (NO) levels, highlighting its antioxidant properties [114,150], which may also contribute to its ability to inhibit RA.

4.1.1.6 Protocatechuic acid.

Protocatechuic acid (PRA), also known as 3,4-dihydroxybenzoic acid, is a widely distributed natural phenolic compound. It is abundant in common vegetables, fruits, cereals, teas, and certain plant-based beverages. PRA is also found in some herbs and traditional Chinese medicines, such as Nidus vespae, Huangqi-Guizhi-Wuwu-Decoction, and Eucommia ulmoides [153]. In whole grains, PRA is present primarily in sorghum and is distributed across the layers of the pericarp, testa layer, and aleurone of sorghum grains [154]. PRA has been demonstrated to have therapeutic effects on gastrointestinal disorders, cardiovascular diseases, diabetes, and cancer, and is utilized as an effective antioxidant, antimicrobial, and anti-inflammatory agent [155]. PRA directly exerts its antioxidant activity through its ability to scavenge free radicals, prevent deoxyribonucleic acid (DNA) oxidative damage, and reduce lipid peroxidation. Additionally, PRA indirectly acts as an antioxidant by inducing endogenous defense systems involving antioxidant enzymes and nonenzymatic antioxidants, which play crucial roles in protecting cells against oxidative damage [156].

Studies on CFA-treated rats have shown that PRA protected against RA by reducing the relative abundance of the inflammatory microbiota, thereby decreasing paw swelling and arthritis scores [157]. Moreover, the viability, migration, and invasion of FLSs were dramatically suppressed by PRA stimulation [158]. PRA, in combination with moupinamide, 6-paradol, and hydrocinnamic acid, inhibited the levels of the RA-related inflammatory cytokines IL-1β, IL-6, IL-7, IL-23, and TNF-α by targeting the cAMP, phosphatidyl-inositol 3-kinase (PI3K)/protein kinase B (Akt), and hypoxia-inducible factor 1-α pathways [157,159]. Additionally, the traditional Chinese medicine Nidus vespae, which contains PRA as a principal bioactive component, also yields similar results that the expression of the inflammatory factors was inhibited through the NF-κB, Akt/mammalian target of rapamycin (mTOR), and nuclear factor erythroid 2–related factor 2 (Nrf2)/Kelch-like ECH-associated protein 1 (Keap1) signaling pathways, resulting in suppressed FLSs viability, proliferation, invasion, and migration ability [158,160].

4.1.2 Flavonoids

The main categories of flavonoid compounds include flavanols, flavones, flavanones, flavonols, anthocyanins, isoflavones, and chalcones. Rutin, quercetin and epicatechin are popular bioactive substances that are abundant in green leafy vegetables, fruits, and grains[161]. Flavonoids possess a basic 15-carbon flavonoid skeleton with a C6-C3-C6 structure, where two phenyl rings (rings A and B) are connected by a

three-carbon pyran ring (ring C) [162]. Flavonoids exhibit various biological activities, including antioxidant, anti-inflammatory, antimicrobial, anticancer, and immunomodulatory properties[161]. In particular, the position of the B-ring catechol on the pyran C-ring, as well as the number and position of the hydroxyl groups on the B-ring catechol, significantly influences the antioxidant capacity of flavonoids [162]. Furthermore, flavonoids exert their antioxidant effects through multiple pathways, including directly scavenging ROS with hydroxyl radicals, chelating trace elements, inhibiting enzyme activity, activating antioxidant defenses, and modulating the Nrf2 signaling pathway, thereby protecting cells from free radical-induced harm [162,163]. Moreover, flavonoids inhibit enzymes such as protein kinases and phosphodiesterases; regulate transcription factors related to inflammatory mediators; and modulate immune cell activity (e.g., inhibiting cell activation, maturation, signaling, and secretion) [164,165].

4.1.2.1 Quercetin.

Quercetin (QUE) is an aglycone, which means that it is a glycoside without a bound sugar moiety. QUE glycosides are formed by the attachment of a sugar group (such as glucose, rhamnose, or rutinose) as a substitute for an OH group, typically at the 3-position. The attached sugar group can alter the solubility, absorption, and *in vivo* effects of QUE [166]. QUE is widely distributed in wine, vegetables, tea, and fruits and is also found in certain whole grains, such as corn, buckwheat, and tartary buckwheat [167-169]. It has a variety of medicinal properties, including antiallergic, anti-inflammatory, anticancer, cardiovascular protective, antitumor, antiviral, antidiabetic, immunomodulatory, antihypertensive, and gastroprotective effects[169].

Clinical trials have shown that QUE plays a crucial role in the treatment of RA. Supplementation with 500 mg of QUE daily for eight weeks significantly relieved clinical symptoms, including early morning stiffness, morning pain, and after-activity pain, and lowered disease activity in 50 female RA patients[170]. Studies on CIA and CFA mice further demonstrated its potential effect on RA, as treatment with QUE three times per week significantly reduced knee joint inflammation-related clinical scores, cartilage damage, and vascular formation, as well as lowering RA biomarkers such as RF, CRP, and anti-cyclic citrullinated peptide[171-173].

QUE primarily affects RA through macrophages. Research on CIA and AIA rats has shown that the antiarthritic effects of QUE are associated with significant reductions in the levels of inflammatory mediators, including TNF-α, IL-1β, MCP-1, NO, and PGE2, produced by peritoneal macrophages[174,175]. Additionally, QUE exhibited immunomodulatory effects by regulating the Th17/Treg balance and Th17 cell differentiation, reducing autoantibody levels, and modulating adenosine deaminase (ADA) activity[173,176]. Like the effects of GA and CGA on arthritis, QUE also affects FLSs, as it suppresses FLS inflammation by inhibiting the production of the inflammatory cytokines IL-1β, IL-6, and IL-8 in TNF-α-induced FLSs[177]. In particular, noncoding RNAs have been shown to be involved in the significant suppression of FLSs migration and invasion by QUE via increasing miR-146a levels and inhibiting the expression of GATA transcription factor 6 in FLSs [178]. In addition, PI3K/Akt, B-cell lymphoma (Bcl)-2/Bcl-2-associated X

protein (Bax), and mitochondrial pathways also mediate the effects of QUE on FLSs, with the upregulation of long noncoding RNA metastasis-associated lung adenocarcinoma transcript 1 [179,180].

Through its ability to suppress Th17 cells, QUE further decreases RANKL protein levels, thereby inhibiting osteoclast formation [181,182]. Moreover, purified QUE improved inflammation by downregulating ADA gene expression, inhibiting neutrophil infiltration, promoting the apoptosis of activated neutrophils, and reducing the levels of the inflammatory cytokines IL-1β, IL-6, and TNF-α in CFA-treated mice [171,172,176,183].

4.1.2.2 Rutin.

Rutin is a flavonol that is abundant in plants such as passionflower, buckwheat, tea, and apple [184]. In whole grains, rutin was distributed in both buckwheat seeds and Tartary buckwheat. It can be detected throughout various parts of buckwheat, including the leaves, flowers, stems, and seeds [185]. Extensive experimental research has demonstrated its significant pharmacological activities, including antioxidant, anti-inflammatory, antidiabetic, antiobesity, neuroprotective, and hormone-regulatory effects [186].

Rutin exhibits potent anti-inflammatory and antioxidant properties by alleviating symptoms and improving tissue pathological changes both *in vivo* and *in vitro*. Rutin significantly reduced the production of TNF-α, IL-1β, MMP-2, and MMP-9 through the activation of SIRT1, leading to decreased expression of NF-κB and MAPK. This subsequently inhibited the activation of COX-2 and iNOS, thereby reducing oxidative stress in rat chondrocytes [187,188]. Research on CFA-treated rat models further demonstrated its antioxidant properties, with rutin displaying strong free radical scavenging activity and increasing the levels of superoxidase dismutase, glutathione peroxidase (GPx), and glutathione (GSH) in a dose-dependent manner. Additionally, rutin inhibited the levels of the inflammatory and oxidative stress mediators TNF-α, IL-1β, IL-6, MDA, NO, and PGE2, as well as NF-κB p65 protein expression, resulting in reduced bone erosion and improved synovial hyperplasia, pannus formation, and cartilage formation, thereby offering protective effects against RA [189,190].

4.1.3 Avenanthramides

Avns are a unique group of phenolic alkaloid compounds in whole-grain oats and are predominantly found in oat bran and oatmeal, with typical concentrations in regular oats ranging from 0.55 to 775.5 mg/kg (fresh weight) [191]. Avns play crucial roles in the prevention of chronic diseases, including immune modulation, antimicrobial effects, dermatological conditions, neuronal protection, lipoxygenase inhibition, and lipid metabolism. Additionally, Avns have been shown to prevent cancer by inhibiting active substances and regulating cellular and molecular events at various stages of cancer development[192].

Numerous studies have confirmed that Avns exhibit potent anti-inflammatory and antioxidant properties. A previous study revealed that Avns treatment suppressed PGE2 production and exhibited COX-independent anti-proliferative effects in macrophages [193]. Another study demonstrated that Avns selectively reduced IL-6 secretion and MMP-9 enzyme activity via the MAPK/NF-κB signaling pathway,

inhibiting NF-κB nuclear translocation in TNF-α-stimulated human arterial smooth muscle cells, indicating the roles of Avns in the anti-inflammatory process [194]. Furthermore, long-term Avns supplementation significantly reduces the serum levels of GPx, GSH, and ROS, leading to increased antioxidant capacity [195]. In particular, Avns has been demonstrated to suppress the expression of inflammatory mediators in the blood and inhibit cartilage degradation. A study on osteoarthritis mouse models showed that Avns inhibited the expression of MMPs (including MMP-3, -12, and -13) via p38 kinase and c-Jun N-terminal kinase signaling pathways leading to reduced cartilage degradation [196]. Therefore, Avns has potential therapeutic effects on RA treatment, although extensive population studies are still needed.

4.2 The potential role of nutrients from whole grains in regulating RA

The bran and germ of whole grains are rich in a wide range of nutrients, including compounds such as dietary fiber, vitamins and various minerals, whereas the endosperm of whole grains consists mainly of starch and small amounts of vitamins, minerals and proteins [98,197]. Therefore, the grain refining process results in the loss of a large amount of such nutrients. Taking dietary fiber as an example, up to 75% of the DF content can be lost during the refining process of grains [98]. These nutrients may play a role in RA by regulating the gut microbiota, modulating the immune system and reducing inflammation [198,199], and details of the relevant human and animal experiments related to nutrients are provided in Table 4.

Table 4. Suppression of rheumatoid arthritis by nutrients in whole grain.

Nutrient Name	Dose/Duration	Animal Model/Cell line	Mechanism	Ref.
Dietary fiber	high-fiber bars or cereals/28 days	human/RA	SCFAs↑	205
Dietary fiber	high-fiber bars or cereals/28 days	human/RA	Circulating regulatory T-cell numbers, favorable Th1/Th17 ratios↑; Total serum immunoglobulin A, HAQ, CRP↓	206
Dietary fiber	high-fiber diet/30 days	rat/CIA	IL-6, IL-17, IL4, IFN-α, RF↓	208
α -tocopherol (vitamin E)	600 mg twice a day/12 weeks	human/RA	Joint discomfort, swelling and stiffness↓	213
Vitamin E	400 mg/3 months	human/RA	TNF-α↓	214
rac-α-tocopherol (vitamin E)	5 mg/6 days	rat/Macrophages	MIF, IL-2, IL-6↓	216
Hydroxocobalamin (vitamin B_{12})	100 mg/kg	rat/CIA	IL17A, TNFα, IL-6, COX-2, ANXA2, PADI-4↓	225

Notes: RA: rheumatoid arthritis; CIA: collagen-induced arthritis; MIF: migration inhibitory factor; TNF: tumor necrosis factor; IL: interleukin; COX: cyclooxygenase; ANXA2: annexin A2; PADI-4: peptidylarginine deiminase isoform 4; SCFAs: short-chain fatty acids; HAQ: health assessment questionnaire; CRP: C-reactive protein; Th: T helper cell; IFN: interferon; RF: rheumatoid factor.

4.2.1 Dietary Fiber

DF is an important component of whole grains and can be classified into soluble dietary fiber (SDF) and insoluble dietary fiber (IDF). IDF is a structural component of plant cell walls that is composed of cellulose, insoluble hemicellulose, and lignin, whereas SDF consists of a variety of noncellulosic polysaccharides and oligosaccharides, such as pectins and β-glucans [200]. The majority of IDF is found

primarily in the bran and husks of grains, resulting in a significantly higher DF content in whole grains than in refined grains [201]. In whole grains, the total DF content is highest in oats, barley, and rye, with values ranging from 10.3-37.7 g/100 g (on a dry matter basis), 10.1-27.9 g/100 g (on a dry matter basis), and 14.7-20.9 g/100 g (on a dry matter basis), respectively [197]. Indigestible DF is fermented by the gut microbiota to produce SCFAs, which can influence the integrity of the intestinal epithelium and mucosal barrier, the immune response, and the diversity of the human microbiome, thereby potentially affecting RA [202,203].

Recent studies have confirmed a significant inverse relationship between increased total fiber intake, particularly an increase of 5 g/day, and the incidence of RA, with cereal fiber intake as the primary mitigating factor [204]. In studies involving 36 RA patients receiving standard treatment, daily intake of high-fiber bars or cereals for 28 days significantly increased beneficial microbial metabolites such as SCFAs, particularly acetate and butyrate, which were associated with a reduction in patients' HAQ scores, CRP levels, and total serum immunoglobulin A content [205,206]. Furthermore, studies showed that feeding mice a high-fiber diet led to an increase in tolerogenic $CD103^+$ DCs, which subsequently enhanced the differentiation of regulatory T cells (Tregs), resulting in reduced inflammation and bone erosion [207]. A high-fiber diet also increased fecal butyrate abundance and remodeled the metabolic profile of $CD4^+$ T cells in an AMPK-dependent manner while also inhibited proinflammatory cytokines such as IL-6, IL-17, IL-4, and IFN-α, thereby improving the inflammatory response in CIA rats [206,208]. Additionally, research showed that inulin enhanced LPS-induced IL-6 production, thereby promoting macrophage activation and antigen presentation, while the consumption of fermentable DFs, such as inulin, alleviated inflammation *in vivo*, thereby inhibiting the expression of proinflammatory genes in the colon [209]. These results indicate the potential role of DF in RA treatment and prevention.

4.2.2 Vitamins

4.2.2.1 Vitamin E.

Vitamin E is a collective term for four tocopherols (α-, β-, γ-, and δ-tocopherols) and four tocotrienols (α-, β-, γ-, and δ-tocotrienols). The primary dietary source of vitamin E is vegetable oils, with whole grains also serving as a good source [210]. Among whole grains, barley and soft wheat have the highest total vitamin E contents, at (75 ± 13) mg/kg dry weight and 74 mg/kg dry weight, respectively, whereas spelt has the lowest total vitamin E content, at (57 ± 8) mg/kg dry weight [211]. The most important function of vitamin E in the body is its antioxidant activity and its role in maintaining membrane integrity. The free hydroxyl group on its aromatic ring is responsible for its antioxidant property, as the hydrogen atom from this group can be donated to free radicals, resulting in the formation of a resonance-stabilized vitamin E radical [212]. Vitamin E has also been shown to play a role in immune function, DNA repair, and other metabolic processes [212].

Vitamin E has been shown to be beneficial for treating RA. In a study involving 42 RA patients, a daily dose of 600 mg of α-tocopherol administered twice daily for 12 weeks helped reduce joint discomfort,

swelling and stiffness, thereby improving the overall quality of life of RA patients [213]. A randomized controlled trial involving 78 patients with RA for at least two years reported that daily supplementation with 400 mg of vitamin E significantly reduced TNF-α levels in patients [214]. Further studies on rats with CFA-induced arthritis demonstrated that α-tocopherol reduced hind paw swelling, leukocyte infiltration, and the mRNA expression of proinflammatory cytokines in the anterior tibial muscle while also lowering the elevated levels of reactive oxygen species in the brain and liver [215]. Furthermore, vitamin E has anti-inflammatory and immunoregulatory effects. Studies showed that vitamin E treatment regulated macrophage migration inhibitory factors and inhibited the inflammatory cytokines IL-6 and TNF-α, thereby suppressing macrophage activation in rats [216]. The inhibition of PGE2 production by macrophages is considered as one of the mechanisms by which vitamin E improves T-cell-mediated immune responses. Vitamin E administration also improved the decline in T-cell function and increased redistribution of activated T cells to immune synapses in aged mice by reducing PGE2 production by macrophages [210,217,218]. In addition, vitamin E-enriched diets have the potential to modulate NK cell activity and Treg cell properties, as well as the interactions between these two cell types [219]. Moreover, the ability of vitamin E to restore the intestinal barrier and improve gastrointestinal function may be relevant to the prevention and treatment of RA [220]. Since both inflammation and immune disorders are closely related to RA progression, these effects of vitamin E may contribute to the management of RA.

4.2.2.2 B vitamins.

B vitamins are essential micronutrients in numerous metabolic and regulatory processes in the human body. They act as cofactors for hundreds of enzymes and play fundamental roles in energy metabolism, DNA and protein synthesis, and other critical activities [221]. B vitamins are widely distributed in whole grains, such as whole wheat, and are concentrated in bran and germ, particularly [221]. Like vitamin E, B vitamins play crucial roles in RA by inhibiting inflammation, reducing ROS and regulating the immune system. For example, vitamins B_1 and B_6 prevented excessive production of neutrophil extracellular traps in inflammatory diseases via regulating transketolase activity, thereby inhibiting ROS release in a dose-dependent manner. Further studies showed that NF-κB activity were inhibited with B vitamins administration [223,224]. Studies have also shown that vitamin B_{12} ameliorated RA in CIA mice [225]. RA was associated with citrullination, a process catalyzed by peptidyl arginine deiminase type 4 (PADI-4) [226], which was recently identified as a new target of vitamin B_{12}, indicating that vitamin B_{12} might relieve RA via this process. Moreover, vitamin B_{12} was shown to inhibit the gene expression of RF, IL-17A, TNF-α, IL-6, and COX-II [225]. These results indicate the potential roles of B vitamins, especially vitamins B_1, B_6 and B_{12}, in the treatment of RA.

4.2.3 Minerals

Grains contain mineral elements such as potassium, sodium, calcium, iron, and zinc[227]. For example, the seeds of quinoa have significantly higher contents of potassium (927 mg/100 g), calcium (149 mg/100

g), magnesium (250 mg/100 g), phosphorus (384 mg/100 g), sulfur (150-220 mg/100 g), iron (13.2 mg/100 g), and zinc (4.4 mg/100 g) than those of wheat and rice. Phosphorus, potassium, and magnesium are found in the germ of quinoa, whereas calcium and phosphorus are mainly present in its husk [228]. Whole grains, with the germ and husk intact, are rich in minerals compared with refined grains. Supplementing these minerals has been shown to prevent and slow the progression of RA, as high oral potassium intake, which is based on an appropriate vegetarian diet and food supplements, significantly alleviated joint pain and improved RA symptoms in a 16-week clinical study involving 172 adult patients with RA [229].

Whole grains such as wheat and rye are good sources of zinc. Zinc is distributed throughout all body tissues and organs as well as body fluids. In adults, the total zinc concentration is approximately 2-3 g, with 85% found in muscles and bones [230]. Adequate zinc intake is crucial for both innate and adaptive immune system functions and is especially beneficial for RA. Some studies have compared and evaluated the changes in trace element concentrations in the synovial fluid and plasma of RA and OA patients and reported that zinc deficiency in RA patients was associated with increased expression of IL-1β, IL-1α, and IL-6. Experimental results suggest that zinc might regulate the expression of TNF-α, IL-1β, and IL-6, inhibit osteoclast proliferation, alleviate inflammatory responses, and positively impact the occurrence of RA [231]. Additionally, some experiments have shown that zinc supplementation promotes the development of immune cells. Zinc maturation and function play crucial roles in T-cell formation [232], ensuring antibody production, enhancing resistance, reducing infections, and improving subjective symptoms such as joint swelling and morning stiffness. Zinc also helps maintain a normal appetite and promotes the absorption of nutrients, while zinc deficiency may lead to loss of taste, anorexia, partial eating, or abnormal eating, and dysbiosis in the gut microbiota, which indirectly regulates the body's immune system and thus contributes to the alleviation and treatment of RA [233].

5. Conclusion

As an autoimmune disease, RA has lacked a curative treatment, necessitating the exploration of new prevention and treatment strategies. Recently, although progress has been made revealing a critical role for whole-grain intake on health improvement, the effect of whole grains on RA alleviation remains unclear. In this article, we summarized clinical and pre-clinical studies on the alleviation of RA by intervention with whole grains and their components, and highlighted their potential mechanisms in RA administration. There has been only few Clinical trial focusing on the role of whole-grain supplementation in RA management. However, both *in vivo* and *in vitro* studies have revealed that polyphenolic phytochemicals abundant in whole grains, such as phenolic acids and flavonoids, alleviated RA via mitigating systemic and local inflammatory responses, downregulating the proliferation and migration of synovial fibroblasts, and inhibiting cartilage degradation. These compounds show the potential as both natural agents and part of whole-grain enriched foods for the prevention and management of RA. Clearly, much more work is required to explore and validate their dose-effect relationships and impacts on patients with RA. Additionally,

nutrients in whole grains, such as dietary fiber, vitamins, and minerals, also contribute to immune function regulation and inflammation suppression, indicating their potential effects on managing RA. Therefore, we anticipate that nutritional interventions involving whole grains and their components might be beneficial for suppressing RA, offering a novel approach for its prevention and treatment.

Disclosure statement

The authors declare no conflicts of interest.

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