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Review article

Food-derived bioactive peptides potentiating therapeutic intervention in rheumatoid arthritis

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease that affects the joints of the human body and is projected to have a prevalence age-standardized rate of 1.5 million new cases worldwide by 2030. Several conventional and non-conventional preventive and therapeutic interventions have been suggested but they have their side effects including nausea, abdominal pain, liver damage, ulcers, heightened blood pressure, coagulation, and bleeding. Interestingly, several food-derived peptides (FDPs) from both plant and animal sources are increasingly gaining a reputation for their potential in the management or therapy of RA with little or no side effects. In this review, the concept of inflammation, its major types (acute and chronic), and RA identified as a chronic type were discussed based on its pathogenesis and pathophysiology. The conventional treatment options for RA were briefly outlined as the backdrop of introducing the FDPs that potentiate therapeutic effects in the management of RA.

1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease that affects the human body's joints. This immune disease can start at any given stage of life and has no cure yet. The latest data and figures from the World Health Organization (WHO) as of June 2023 show that 18 million people on earth have RA as of 2019, spread between around 70 % of women, 55 % of whom are older than 55 years [1]. If not treated, RA is notorious for damaging the joints and their surrounding tissue with protrusions leading to the lungs, nervous, or heart problems. The symptoms associated with RA include stiffness, heat, swelling of joints, chronic pain, and tenderness. Nonetheless, the causes of RA are yet to be unraveled although air pollution, smoking, and obesity have been identified as some of the risk factors associated with the disease. It is also noteworthy to point out that the population group at the highest risk of RA are women and older people [1]. The parts of the body most often affected by RA are the joints of elbows, shoulders, wrists, hands,

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knees, ankles, and feet, among several other body systems [2]. Cieza et al. [3] suggested that 13 million RA patients could be rehabilitated according to the severity levels of RA that they experience.

To combat RA, several conventional and non-conventional preventive and therapeutic interventions have been put forward. The strategies for the prevention and progression of RA include reduced exposure to dust, silica, and lifestyle-related behaviours. Koller-Smith and colleagues [4] recently proved that breastfeeding could protect a nursing mother with RA. However, to treat RA is where the problem lies because it is not a curable disease. The WHO indeed suggests that its management could involve various health workers who contribute to the personalized rehabilitative treatment of the patients. Among several other recommendations (e.g., weight loss, proper exercise, physical therapy, and the use of crutches and knee pads), are diet control, medicines, or alternatives that can reduce inflammation, pain, and swelling. The most famous conventional of the suggested medicines are non-steroidal anti-inflammatory drugs (NSAIDs) glucocorticoids disease-modifying antirheumatic drugs (DMARDs). These have their limitations and side effects including abdominal pain, nausea, liver damage, ulcers, heightened blood pressure, coagulation, and bleeding with nephrotoxic potential [5–7].

Interestingly, several food-based substances or nutrients are increasingly gaining a reputation for their potential in the management or therapy of RA. The good thing about this is that food substances could be bioactive other than just providing the energy requirement of the body. Of the food products, food-derived proteins champion this campaign because several of their peptides reportedly show multifarious bioactivities [8–10]. They have been identified and structurally characterized to the point that they are shown to rarely show side effects and are safe as both functional food ingredients and nutripharmaceuticals targeting human health improvement [11]. Thus, food-derived peptides (FDPs) potentiate great anti-inflammatory therapeutic effects. They can be produced through enzymatic hydrolysis, which is the commonest, safest, and one of the most efficient methods of producing bioactive peptides. These peptides are usually 2–20 long amino acids in sequence with certain bioactivities that their parental proteins from plant or animal sources lack. Based on their sequence and structural conformations, they exert antioxidant and anti-inflammatory activities, among other bio-functional attributes as they show the ability to repair cartilage cells, relieve inflammation, and intervene in the biological process of bone marrow mesenchymal stem cells (such as differentiation, cell migration, proliferation, and apoptosis) to confer therapeutic effects on bone-related diseases like RA [12,13]. In this review, therefore, we first discussed the concept of inflammation, and its major types vis-à-vis acute and chronic. This leads us to identify RA as a chronic type of inflammation that deserves attention and comprehension of its pathogenesis and pathophysiology. The conventional treatment options for RA were briefly outlined as the backdrop of introducing the FDPs that potentiate therapeutic effects in the management of RA. Scopus, Web of Science, and PubMed are among the electronic databases used in the literature selection. Both published original and review papers focusing on peptides that are used in chronic diseases and rheumatoid arthritis was considered in the search. The search and selection procedure were conducted between January and May 2023, while considering the publications that span the past 15 years but putting more emphasis on the most recently published papers within the past 5 years. As several references were generated during the evaluation, their relevance was determined by examining the titles, abstracts, and keywords in each of them, including but not limited to “peptides”, “rheumatoid arthritis”, “chronic inflammation”, “food-derived peptides”, and “therapeutic peptides”. About one hundred and sixty selected articles were only included after the screening.

2. Overview of inflammation in humans and its types

2.1. Inflammation

Inflammation, from an immunological standpoint, is a local reaction as a result of a variety of infectious agents as well as pathogenic shocks that incite an organism, ultimately causing damage to cells. The innate immune functions establish and actualize this process in the system [14]. The mechanisms causing acute or chronic systemic inflammation, which can result in a variety of diseases, including cancer and cardiovascular disease (CVD), are not well-known. These inflammatory states do not appear to be brought on by the usual sources of inflammation, such as infection or injury, which induces redness, swelling, and pain, including heat characterized by tumors and occasionally rubor [15]. As opposed to being connected to host defense or tissue repair, inflammatory states are tied to tissue malfunction and a loss of homeostatic imbalance of one or several physiological systems [16,17]. Also, saturated fats in meat and full dairy products are connected to the development of inflammation [18]. Inflammation has a critical physiological function in the immune response by protecting against potential pathogenic attacks. An array of metabolic processes is triggered by inflammation to eliminate these external factors and repair any damage they may have caused [14,19,20]. Inflammation that happens when there is no injury or invader can harm healthy parts of the body and predispose them to chronic diseases [21]. As a result, it is crucial to reduce inflammation. Pattern recognition receptors (PRRs) are encoded in the germline and are present on the surface of host cells. The PRRs can detect pathogen structures, evolutionary conserved pathogen-associated molecular patterns (PAMPs), or external stress signals, known as danger-associated molecular patterns (DAMPs), which trigger inflammation.[22,23].

The synthesis of cytokines and chemokines, which are pro-inflammatory, consequently stimulates cellular inflammatory processes. In addition to increasing the permeability of the vascular system and facilitating immune cell entry into infected organs, cytokines can activate endothelial cells, which can result in capillary leakage, vasodilation, and hypotension [24,25]. Chemokines’ primary role is to draw more immune cells to the infection site [26], particularly neutrophils, which are essential for the phagocytosis and eradication of pathogens [27,28]. Neutrophils are activated by TH1-derived IFN-, whereas epithelial cells are stimulated to produce and release antimicrobial peptides (AMPs), such as defensins by the innate lymphoid cells derived IL-22 and TH17 [29]. Activated monocytes and neutrophils discharge cytokines into the bloodstream, and subsequently trigger the discharge of prostaglandins. This mechanism mediates signs and symptoms of disease such as somnolence, weariness, and fever, through hypothalamic perturbation [30]. The activation of the complement system facilitates microbial opsonization and death, and inflammatory peptide production like C3a and

C5a, the crucial aspects of inflammation in the circulation [31].

Numerous systems prevent inflammation. For instance, IL-10 majorly produced by regulatory T cells, inhibits the synthesis of proinflammatory cytokines [32,33]. Inflammation is often suppressed by IL-37 and TGF produced by platelets and monocytes [34]. Cytokine receptors with cleaved extracellular domains, like soluble IL-1R and TNFR, reduce inflammation through interaction, thus neutralizing the corresponding cytokine. The metabolic activity of IL-1R and IL-1 is inhibited by receptor antagonists, e.g., IL-1R antagonist (IL-1Ra), which binds IL-1R without generating intracellular signals [35]. Lipid mediators and Prostaglandins such as resolvins modulate negative feedback patterns through the reduction of transcription rates and cytokine release, including complementing inhibitors by controlled inflammation [36]. AAT and other acute-phase proteins that are produced during inflammation have extensive anti-inflammatory properties [37]. Stress hormones, such as corticosteroids and catecholamines, including negative TLR signaling regulators e.g., IRAK-M and A20, and miRNAs like miR-125 and miR-146 are also anti-inflammatory pathways. By releasing norepinephrine from the spleen and acetylcholine secretion, a subset of $CD4^+$ T cells and neuro-immuno-regulatory mechanisms (also known as the immune reflex) gives negative anti-inflammatory feedback, which peripheral sensory input generated and transmitted via afferent vagus nerve into the brainstem. This inhibits proinflammatory cytokines production by macrophages. On the other hand, a host may become susceptible to subsequent infections if anti-inflammatory responses are overly strong or continuous [38].

2.2. Types of inflammation

2.2.1. Acute inflammation

A series of events occur in an acute type of inflammation. Pro-inflammatory cytokines that have been released can cause an inflammatory loop form that causes separation from injured tissue to enter the bloodstream, which results in a situation known as a "cytokine storm." One of the several cytokines implicated in this process is TNF [39,40]. These cytokines cause a systemic response by activating organ-specific receptors. Increase in the production of certain proteins, such as C-reactive protein, haptoglobin, α-globulins with antiprotease-activity, ceruloplasmin, fibrinogen, serum amyloid A complement factor- 3, and lipopolysaccharide-binding protein is ensured by the liver. This leads to a decrease in the serum quantities of retinol-binding protein, iron, transferrin, zinc, albumin, transthyretin, transferrin, and cortisol-binding globulin. The explicit reason for each of the changes in protein concentration is yet to be known, however, scavenging pathogens modulating the inflammatory response including its concomitant patterns may be very noteworthy [41,42]. C-reactive protein remains the best clinical predictor of the acute-phase response despite its indifference to the causes of inflammation [43–46].

The brain endothelium is another location where circulating cytokines exert their effects, causing the release of prostaglandins that cause fever, anorexia, and lethargy as a beneficial adaptive response to infection [47]. Muscle atrophy results from additional changes that happen during inflammation, including an increased metabolic rate, muscle catabolism to recover amino acids needed for tissue healing, and protein synthesis for the immunological response to the lesion [45].

2.2.2. Chronic inflammation

On the other hand, chronic inflammation, as found in non-communicable diseases, lacks the characteristics of acute inflammation [48–50]. Acute inflammation is frequently brought on by exogenous sources like infections and is characterized by redness, swelling, fever, and discomfort. Contrarily, endogenous substances or substances released endogenously as a result of tissue damage (also known as endogenous ligands) bind to PRRs of the innate immune system to trigger chronic inflammation [51,52]. Mild inflammation can last for a very long time and result in tissue damage and/or fibrogenesis, which leads to irreversible organ dysfunction [53,54]. For example, enterobacteria's endotoxin LPS can move from the leaky gut into the bloodstream and produce endotoxemia or sepsis [55–58]. This is a type of systemic inflammation, a pathogenic process of Alzheimer's disease, along with a leaky gut [59]. Additionally, as triglycerides break down, accumulated fat cells as a result of obesity release FFAs [18,60]. Inflammatory mediators are produced when LPS and FFAs bind to the monocytes' and macrophages' TLR4. This indicates that obesity contributes to sustained inflammatory cytokines production due to the recruitment of inflammatory cells to the deposited fat, essentially leading to a chronic inflammatory response [60,61].

Inflammation is currently the immune system's way of getting rid of xenobiotics and unidentified endogenous signals [62]. When inflammation is resolved, pathogens are successfully cleared away, but untreated acute inflammation can worsen the condition or develop into chronic inflammation, which is indicated by serum proinflammatory biomarkers like IL-6, C-reactive protein (CRP), TNF-, IL-1, or IFN-Y. Instead of the term "chronic inflammation," researchers from various fields may use terms like systemic chronic inflammation (SCI), "low-grade systemic inflammation", "low-level systemic inflammation" (LLSI), "chronic low-grade inflammatory phenotype", "inflammaging", or "immunosenescence" [63–68].

3. Rheumatoid arthritis: its pathogenesis and pathophysiology

Chronic joint tissue inflammation is a hallmark of the prevalent autoimmune illness rheumatoid arthritis (RA) [69,70]. Environmental factors, genetics, and infections are thought to contribute to the onset of RA [71,72]. Small joints, notably interphalangeal joints and wrist joints, are swollen, painful, and deformed in around half of the patients [73]. Advanced cases may show joint deformation and functional restrictions, and some significant internal organs, including the lungs, heart, kidneys, and digestive tract, may also be affected. This condition is a major health concern around the world and places a heavy psychological burden on patients as well as a financial burden on many affluent societies [73,74]. Musculoskeletal pain, edema, and stiffness are frequent clinical practice

complaints, making knowledge of RA diagnosis and treatment essential. RA patients are more likely than the general population to have major infections, respiratory conditions, osteoporosis, cardiovascular diseases, cancer, and death. Recent improvements in RA care and long-term prognosis include early diagnosis, intensive treatment, and wider therapeutic options of disease-modifying anti-rheumatic medications [75].

Studies examining joint tissues during the preclinical phase have indicated that the early stages of RA, despite evidence that plasma cells in the synovia can produce autoantibodies in patients with developed RA, do not appear to impact the synovia [76,77]. Subjects with no clinically obvious synovitis, but with autoantibodies related to serum, do not indicate synovial inflammation in their knee joints when subjected to histological and magnetic resonance imaging (MRI) [78]. With MRI, ultrasound, and positron emission tomography (PET), joint symptoms of "arthralgia" and no clinically obvious synovitis were detected, in a small population of people with serum anti-citrullinated protein antibodies (ACPAs), signifying there was no subclinical joint inflammation [79].

Patients with RA may have synovial tissue that is classified as either ectopic lymphoid structures (ELS) or tertiary lymphoid tissue (TLT). The secondary lymphoid tissue (SLT), the site for T cell and B cell differentiation, is similar to this structure. TLTs are linked to continuous inflammation in RA because they correlate with inflammatory cytokine levels, disease severity, and autoantibody titers in RA patients [80]. RA patients have two important pathogenetic changes in their synovial membrane. Regarding the first, both synoviocyte types—macrophage-like synoviocytes (MLSs) and fibroblast-like synoviocytes (FLSs)—are increased and activated, resulting in a significant expansion of the intima. These synoviocyte types are important sources of proteases e.g., integrins, selectins, and cytokines as well as the immunoglobulin superfamily members. Numerous pro-inflammatory cytokines, such as IL-6, IL-1, and TNF are produced by MLSs [81]. FLSs in addition, IL-6 expresses matrix metalloproteinases (MMPs) and some small-molecule mediators such as prostaglandins and leukotrienes which encourages the creation of ELS in synovial tissues and interact with immune cells to help activate immunological responses [82,83]. The adaptive immune cell which is the second, infiltrates into the synovial sub-lining which leads to the development of a recognizable “pannus” at the cartilage-bone contacts [84]. The Pannus, which is made up of mast cells, FLSs, dendritic or plasma cells, and macrophages, causes erosion formation and damage in later disease [85,86].

The $CD4^+$ memory T cells that make up half of the sub-lining cells diffusely infiltrate organs or create ectopic germ centers, a site for multiplication, development, and manufacture of antibodies by matured B cells [87]. Additionally, B cells, plasma blasts, and plasma cells do exist and they are capable of producing rheumatoid factors (RFs) or ACPAs [88]. The most common antibody present in the mucosal immune system is IgA and may elicit RA-related autoimmunity at this site. Data has shown that IgA-ACPAs were increased and highly specific in the early clinical and preclinical stages of RA [89–91]. According to research on certain mucosal sites such as the oral cavity, lungs, and gut, the environment seems to influence and play a major role in altering and activating the mucosal site (i.e., the GI or genitourinary mucosa) [92].

Reports have shown that oral mucosa is a potential site of RA genesis in recent years, with a focus on the gingiva and periodontal regions. Periodontitis is more common and more severe in RA patients and is connected with RA-related autoantibodies [93–96]. Severe periodontitis is also linked to RA-induced autoantibodies in persons without RA [97]. Additionally, it was shown that the periodontitis-causing bacteria *Porphyromonas gingivalis* expressed the peptidyl-arginine deaminize (PAD) enzyme, which may citrullinate peptides and proteins from humans [98]. In people without RA, a connection between serum RA-related autoantibodies and antibodies to *P. gingival* was discovered, and it has been demonstrated that inflamed gingival tissue expresses higher quantities of PAD and citrullinated proteins [99,100]. Gingival fluid linked to gingivitis was discovered to have regional anti-CCP antibodies. It seems that periodontitis and gingivitis influence the cardiovascular system in addition to acting as a systemic inflammation trigger zone brought on by bacterial infections transmitted locally [101]. To further comprehend the pathogenesis of RA through the participation of oral mucosa, longitudinal studies are required to assess the association of oral infections, the production of gingival autoantibody locally, autoimmunity related to systemic RA, and the inflammation of joints [102,103].

The "mobile microbiome" notion was used to define the systemic transmission of oral infections, their toxins, and their immunosuppressive compounds [104]. This hypothesis could help to explain the development of autoantibodies in infections that are localized in one area but result in distant phenomena such as autoimmune neuropsychiatric disorders linked to polycystic kidney disease, streptococcal infections, obesity, and diabetes mellitus [105]. It is unclear what biological mechanism underlies the connection between systemic illnesses and fecal-oral infections. Proteomics research revealed that there is significant peptide similarity between human cardiovascular autoantigens and bacterial antigens, which may make it possible for bacteria like *Streptococcus mutants* to interact with human heart tissue [106].

The lungs are another mucosal surface that could be affected by autoimmunity in RA. Evidence that smoking increases the chance of developing RA and that the prevalence of disease of the lungs, and airway inflammation, is high in individuals with RA, lend credence to this idea [107–111]. When compared to matched controls who lacked blood RA-related autoantibodies, computed tomographic imaging showed a higher incidence of disease of airway inflammation in people who did not have arthritis (through joint examination in a small sample of subjects, using MRI) [111]. This result was true whether or not a person was currently smoking cigarettes. Fischer and colleagues [109] discovered that imaging evidence of airway inflammation was present in 80 % of people with chronic lung illness who were anti-CCP antibody positive but did not have joint symptoms [112]. Ninety-six percent of these participants showed histologic proof of pulmonary inflammation. Five participants in these two investigations developed synovitis that might be classified as RA. All five had signs of inflammation of the lung before the onset of clinically evident arthritis [112]. In a different investigation, participants without arthritis showed RF which may also include antibodies antagonist of CCPs in their sputum and not the serum, indicating that these autoantibodies related to RA in this population are produced in the lung [113].

The gut microbiome, up to this point, has received a lot of attention in research on the gastrointestinal mucosa composition in RA. The innate and adaptive immune systems’ growth, as well as the onset of autoimmune disease, are both known to be influenced by the gut microbiome [114]. Specific changes in gut bacteria have been shown in murine investigations to either increase or decrease

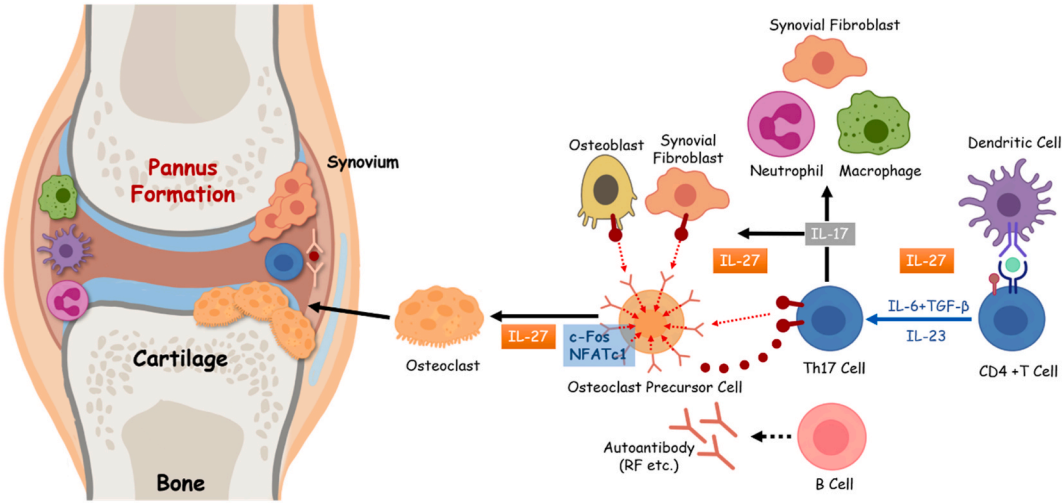

Fig. 1. The mechanisms and pathophysiology of rheumatoid arthritis. IL-27 is a major role player in the regulation of inflammatory immune responses that lead to bone destruction in RA. *Adapted* from Yoshimoto et al. [121].

susceptibility to experimentally induced arthritis [115–118]. Human studies have found variations in the gut microbiota between RA patients and controls [119,120]. However, it is unclear to determine whether variations in gut microbiota communities are caused by an existing inflammatory environment, or if RA treatments are to blame for changing the gut microbial makeup. The corresponding pathophysiology of RA is illustrated in Fig. 1.

4. Conventional treatment of RA

There is no cure for RA presently, although doctors recommend some medications meant to relieve the symptomatic pains that accompany RA. The risk of joint damage and the impact of RA would be drastically reduced when early therapeutic intervention and support are embraced. These may include the prescribed medications, changes to lifestyle, surgery, and other supportive treatments. The general practitioner or particular specialists often make their prescriptions based on stopping RA from getting worse while reducing the risk for other complications. They have to consider the cost of treatment when choosing a treatment option for the patients [122]. They either prescribe either biological treatments or DMARDs. DMARD tablets such as methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine are first prescribed for the first round of treatment to relieve RA symptoms and subsequently stop it from progressing. The drugs' action mechanisms include blocking the effects of released inflammatory cytokines, which are capable of causing more harm to the cartilage, tendons, ligaments, and bones. Biological treatments including etanercept, adalimumab, and infliximab, are more novel and are administered with other DMARD medications like methotrexate. They are recommended only when the effectiveness of DMARDs is in question. They are also mostly intravenously administered unlike the DMARDs, and act by blocking certain pro-inflammatory cytokines in the blood responsible for pains in the joints.

The problems with either of the treatment options include certain side effects like loss of appetite, feeling sick, diarrhea, a sore mouth, hair loss, and headaches. These have been reported in patients more commonly especially with regards to methotrexate. The lungs, liver, and blood cells are not excluded. Sometimes, shortness of breath or a persistent dry cough may be experienced during the regime, not to mention that it may take a few months to notice any effectiveness of a DMARD. For biologics, the side effects are usually milder and include headaches, fever, and skin reactions. However, some patients could develop more serious problems such as a resurgence of previous infections like tuberculosis. Many concerns emerge about possible increases in cardiovascular risk and disease occurrence [123,124]. It is obvious from these conventional treatment options that a more sustainable, much safer, and perhaps food-derived alternative therapy is warranted for treating or managing RA.

5. FDPs in the management of RA

Disease cure and delay processes using selected foods could be achieved. For instance, Li et al. [125] showed that Perilla peptides could delay the progression of kidney disease through apoptotic injury and oxidative stress improvement and maintenance of intestinal barrier function. In this section, we take a look at food-derived bioactive peptides (FDPs) and their potential therapeutic effects on RA based on documented evidence in the literature. Table 1 describes the most recently reported FDPs that have shown prospects in ameliorating RA. While the majority of the studies reported the effects of the FDPs on Osteoarthritis, it can be deduced from the targeted joints and pain relief mechanisms that the effects could have similar impacts on RA. These FDPs could be obtained from either plant or animal sources. Take Lunasin as an example from the plant sources, it is a 43 amino acid sequence polypeptide with 5500-Da molecular weight derived from soybean and has been reported to exert anti-cancer, anti-hypertension, anti-inflammation, and anti-oxidant effects [126]. The study by Dia and colleagues [127] showed that this same Lunasin aids the reduction of IL-1β-mediated

Table 1
Recently reported food-derived peptides potentiating RA management.

Name	Peptide source	Treatment parameters	Observations	Experimental model	Reference
Seahorse protein hydrolysate	Yellow seahorse (*Hippocampus kuda*)	Oral, 4 mg/kg/day, 6 weeks	Plasma proinflammatory factors reduction, along with type II C-telopeptide collagen, and MMP-3 and MMP-13. Knee joint pain relief and decrease in proteoglycan loss and swelling.	Rats	Sudirman et al. [130]
Protein-rich Deer antler extract	Deer	Oral, 0.2 g/kg/day, 3 weeks	Expression levels of functional genes involved in cartilage formation, growth, and repair increased.	Rats	Yao et al. [131]
Native type II collagen	Chicken sternum cartilage	Oral, 0.66 mg/kg/day, 8 weeks.	The weight-bearing capacity of the injured leg and the integrity of the cancellous bone improved. Excessive osteophyte formation and deterioration of articular cartilage were prevented.	Rats	Bagi et al. [132]
Collagen hydrolysates	Fish/Porcine	*In vitro*, 0–10 mg/mL/day, 6 days	The loss of proteoglycan increased while ADAMTS4 was inhibited.	Human cartilage explants from lateral condyles of patients	Schadow et al. [133]
Sternal cartilage hydrolysates	Chicken	Oral, 50–500 mg kg/day	Chondrocyte changes and collagen structure destruction was inhibited.	Rats	Ma et al. [134]
Cartilage hydrolysates	Bovine	Oral, 200 & 500 mg/kg/day	Cartilage degeneration is reduced.	Rats	Hao et al. [135]
Collagen peptides <1.5 kDa	Fish cartilage and skin	*In vitro*, 50–100 μg/mL, 3 days	The synthesis of collagen types I and II was enhanced.	Equine articular chondrocyte organoids	Bourdon et al. [136]
Collagen peptide	Iridescent shark catfish (*Pangasius hypophthalmus*) skin	Oral, 100–200 mg/kg/day, 12 weeks	Cartilage damage and loss of proteoglycan reduced. The deterioration of the microstructure in the tibial subchondral bone was suppressed. Type II collagen was upregulated but matrix metalloproteinase-13 in the cartilage tissue was downregulated.	Rabbits	Lee et al. [137]
Pilose antler (*Cervus elaphus* Linnaeus) peptide	Deer antlers	*In vitro*, 1–128 μM, 24 h	Over-expression of inflammatory factors was inhibited	Nucleus pulposus of the vertebra disc	Dong et al. [138]
Chicken cartilage hydrolysate (Mw < 10 kDa)	Chicken	Oral, 100 mg/kg/day, 30 days	IL-1β, IL-10, TNF-α and MMP-13 levels decreased.	Rats	Yang et al. [139]
Antarctic Krill peptides	Antarctic Krill	Oral, 195–600 mg/kg/day, 8 weeks	Cartilage thickness and area increased.	Rats	Wang et al. [140]
Lunasin	Soybean	*In vitro*, 50 and 100 μM, 48 h	MMP-3 and MMP-13 decreased. TIMP-1 and TIMP-2 expressions increased while the reduction of type II collagen was suppressed.	Chondrocytes	Dai et al. [141]
Collagen peptide	–	Oral, 5 g/day, 12 weeks	Activity-related pain intensity was improved	Athletes with functional knee problems	Zdzieblik et al. [142]
Calcitonin	Salmon	Intra-articular injection, 2.5 and 5.0 IUkg/day, 28 days	Type I collagen, collagen type II α-1, malondialdehyde, uric acid and interleukin-6 decreased. Superoxide dismutase increased.	Rats	Adeyemi and Olayaki [143]
Collagen hydrolysate (<3 kDa, 3–10 kDa, >10 kDa)	Fish	*In vitro,* 100 μg/ml, 0–28 days	Pro-MMP3 and pro-MMP13 were induced while *p*-ERK and p-p38 were activated.	Porcine cartilage explant	Boonmaleerat et al. [144]
Collagen hydrolysate	The skins of cod, haddock, and pollock	Oral, 20 g/day, 16 weeks	MMP-3 levels reduced. Lameness and pain improved.	Dogs	Eckert et al. [145]
Collagen hydrolysate	–	Diet, 3 months	Pain reduced.	Dogs	Comblain et al. [146]
Type I collagen hydrolysate (2 kDa)	Bovine	Oral, 3.8 or 38 mg/day, 12 weeks	The cartilage area, chondrocyte number, and proteoglycan matrix were increased while reducing synovial hyperplasia.	Mice	Dar et al. [147]
Collagen peptides (6 kDa)	–	Oral, 25 g and 50 g/day, 12 weeks	Lameness and flexion pain improved.	Horse	Dobenecker et al. [148]

(*continued on next page*)

Table 1 (*continued*)

Name	Peptide source	Treatment parameters	Observations	Experimental model	Reference
Chicken leg extract digest	Chicken	Oral, 50 mg/day, 3 weeks	Acid mucopolysaccharide production was enhanced and regeneration of cartilage matrix was facilitated.	Rabbits	Yamada et al. [149]
Cervus and Cucumis peptides	Sika deer bone and melon seed	Intravenous injection, 24 mg/day, 7 days	The immunoregulatory function was enhanced.	Patients with RA	Qi et al. [150]
Fish cartilage hydrolysate	Fish	Oral, 103.33 mg/kg, 4 weeks	Pain relief and joint function recovery.	Rats	Henrotin et al. [151]
Collagen hydrolysate (1.45 kDa and 0.57 kDa)	The skin of blue shark (*Prionace glauca*)	*In vitro*, 50–500 μg/mL, 24 h	Collagen type I mRNA increased.	Human dermal fibroblast	Sanchez et al. [152]
Type I collagen hydrolysate (<3 kDa)	Bovine	*In vitro*, 1 mg/mL, 48 h; Intra-articular injection, 4 mg/2 mL/day, 2 weeks	Type-II collagen was induced while inhibiting type-I collagen deposition. Hyaline cartilage was enhanced while preventing fibrous tissue formation in chondrocytes.	Knee of patients	De Luca et al. [153]

chondrocyte proliferation which contributes to improved availability of type II collagen. The authors also observed that the soy peptide inhibited the expressions of MMP-3, MMP-13, TIMP-1, and TIMP-2 [127]. The anti-inflammatory effect of Lunasin was further confirmed by its inhibition of the activation of the JAK2/STAT1/IRF-1 pathway. JAK2 (a non-receptor tyrosine kinase), STAT1, and IRF-1 are Janus kinase, signal transducer and activator of transcription 1, and interferon regulatory factor 1, respectively, and they are crucial transcriptional factors in cell proliferation and inflammation response. Other than Lunasin, several anti-inflammatory FDPs with prospects in RA management have mostly been prepared from soy proteins. The pool of soy protein hydrolysate is rich in di- and tri-peptides. Some researchers found these peptides to be anti-inflammatory when studied in pigs induced with dextran sodium sulfate [128]. The peptides could upregulate ileal $FOXP3^{+}$ Treg response but downregulate interleukin TNF, 1β, interferon-γ, interleukin-17A, and retinoid acid-related orphan receptor C, all of which are inflammatory mediators. If well purified, the responsible peptides could be targeted and identified. For instance, VPY and FLV soy tripeptides were identified as the sole contributors to the suppressive activity of TNF-α and IL-8 in Caco-2 cells, adipocytes, and macrophages [129].

Not only do soy peptides have therapeutic prospects for RA, but peptides derived from other plant-based proteins have also shown potential. Indeed, several plant-based peptides that have been identified as anti-inflammatory or antioxidant in bioactivity portend therapeutic effects on RA, and they include rice, zein, and rapeseed proteins, among others. Qu et al. [154] most recently identified DNIQGITKPAIR, IAFKTNPNSMVSHIAGK, and IGVAMDYSASSKR peptides from broken rice, and reported that they demonstrated excellent anti-inflammatory. These peptides effectively inhibited nitric oxide production and proinflammatory cytokines in LPS-stimulated RAW264.7 murine macrophages. The peptides of zein prevented TNF-α-induced monocyte adhesion to endothelial cells while inhibiting NF-κB activation, thus establishing an anti-inflammatory potential [155]. ROS, lipid peroxides, and vasodilators production was substantially reduced by rapeseed peptides (i.e., LY, RALP, and GHS), which contributed to oxidative stress reduction and subsequent damage to human health [156]. The authors challenged LPS-stimulated RAW264.7 macrophages with the peptides and observed a significant reduction of nitric oxide production, along with other inflammatory cytokines in the likes of TNF-α and IL-6. All these studies involving plant-based FDPs and their potential to modulate or confer anti-inflammatory effects on RA require further consolidating investigations that span across *in vitro*, *in vivo*, and clinical interventions to validate their efficacy and establishment as promising therapeutic agents for RA management. The good side to plant-based FDPs as nutraceuticals is that they have a much lesser carbon footprint essential to mitigate the rising challenge of global warming.

The FDPs obtainable from animal sources are numerous including fish, chicken, bovine, deer, and horse. They have all been quite effective, among which collagen and its derivatives are famous. For instance, Bagi et al. [132] reported that type II collagen peptides from native chicken sternum cartilage when orally administered at 263.0 mg per g along with hydroxyproline at 32.9 mg per g sustained the weight-holding ability of an injured leg, reduced the progression of cartilage destruction, and drastically reduced the C-telopeptide fragments of type II collagen (CTX-II) scores. The scores also decreased in rats with RA when fed with collagen peptides, while inhibiting the expression of MMP-13 and type II collagen loss within the anterior cruciate ligament transection [157]. Other researchers mixed collagen hydrolysate with the extracts of green tea and curcuminoids just to observe a pain reduction in the treated dogs with RA [146]. In a later study, Dobenecker et al. [148] mixed multifarious peptides obtained from type I collagen and administered them to horses that suffered from arthritis at 50 g/day for 6 weeks. The researchers observed that both flexion pain and lameness were significantly alleviated in the horses.

Other than collagen peptides from chicken, those obtained from bovine also showed some promise. A 2000 Da type I collagen peptide aid cartilage enhancement, improved the chondrocytes and contributed to the proteoglycan matrix proportionately [147]. The authors found the same peptide to reduce MMP-13 and TNF mRNA levels, all of which are indicative of anti-inflammatory activity. Another work conducted on the same base identified a fraction of bovine-derived type I collagen peptides less than 3000 Da and found that they could inhibit the same type-I collagen deposit in IL-1β-treated chondrocytes while inducing type II collagen [153]. IL-1β is a pro-inflammatory cytokine, connoting that the inducement of type II collagen could suppress inflammation.

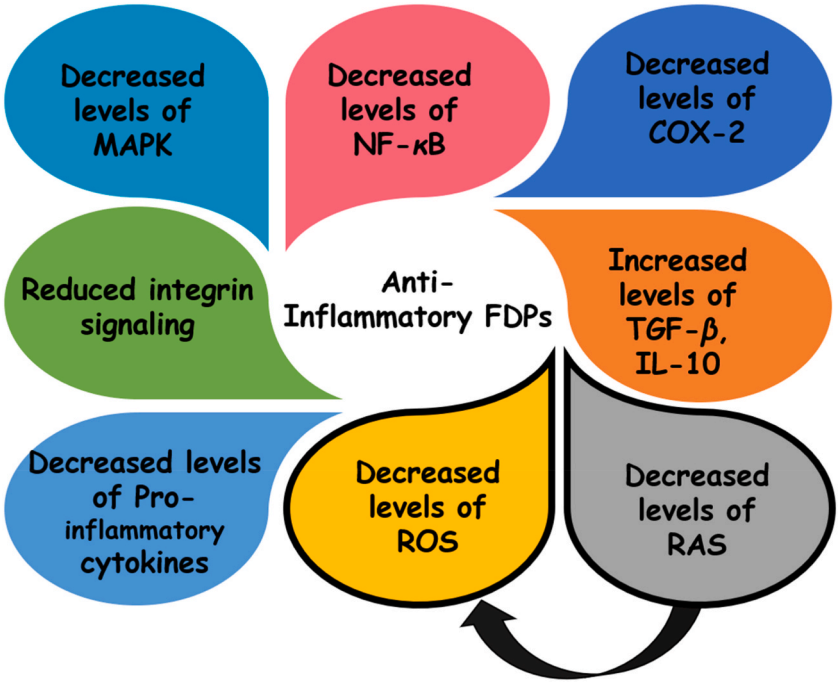

Fig. 2. Possible action mechanisms of food-derived peptides with anti-inflammatory effects. MAPK: mitogen-activated protein kinase; NF-κB: nuclear factor-κB; COX-2: cyclo-oxygenase-2; TGF-beta: transforming growth factor-beta; IL-10: interleukin-10; RAS: renin-angiotensin system; ROS: reactive oxygen species.

The deep-water ocean fish's skin is rich in collagen. It's hydrolysate when administered to arthritic dogs, reduced the levels of MMP-3 and improved their pain and lameness [145]. Fish cartilage and skin peptides also increased types I and II collagen protein synthesis mechanism while suppressing both transcription and expression of inflammatory proteases [136]. The proteases are quite important, making the research an interesting one to be conducted by the researchers. They include ADAMTS5 (A disintegrin and metalloproteinase with thrombospondin motifs 5, which is a key player in aggrecan degradation), HTRA1 (high-temperature requirement A1, a major protease that degrades chondrocytes' pericellular components), and Cox-2 which has an apoptotic effect on chondrocytes. The chondrocytes in turn are directly involved in collagen production and maintaining the joints' cartilages.

Pangasius hypophthalmus's skin collagen peptides also mechanistically reduced inflammation by increasing the expression of the genes of aggrecan and collagen type II alpha chain [137]. The researchers came to this conclusion due to the suppression of tibial subchondral bone microstructural damage, proteoglycan loss reduction, and upregulation and downregulation of type II collagen and MMP-13, respectively in the cartilaginous tissues after oral administration to rabbits. Earlier, Kong and colleagues [158] showed that Walleye pollock skin-derived collagen peptides prevented articular cartilage damage while reducing sera NO and malondialdehyde levels. Most of these studies were intended to find out the potentials of food-derived (in these cases collagen-derived) hydrolysates or active peptides in managing RA, and their efficaciousness using *in vitro* and *in vivo* models. However, more validatory experiments are suggested to affirm the results obtained so far. Possible action mechanisms of food-derived peptides with anti-inflammatory effects are summarized in Fig. 2. These possible mechanisms of anti-inflammation show that FDPs could modulate the RAS (renin-angiotensin system), anti-inflammatory and pro-inflammatory cytokines, pro-inflammatory signaling kinases, integrin-dependent signals, and the production of ROS [159].

6. Further considerations and conclusions

Food-derived peptides show a lot of promises as functional food or nutraceutical agents since they exert important activity such as antioxidant and anti-inflammatory. Nonetheless, the furtherance of research in this regard is necessary before laying hold onto certain health claims like rheumatoid arthritis alleviation. The reason is not far-fetched as verifications of the healthful effects ensure the actualization and commercialization of the experimental results. This is not only good for the economics of chronic NCDs like RA but also helps to control their ever-growing burdens with little or no adverse effects. For RA, its main action mechanism can be correlated with oxidative stress and inflammation, hence the reason for targeting these two phenomena by the FDPs. Some of the studies considered in this review put some signaling pathways forward as possible modulators of RA mediated by FDPs but the clarity and authoritativeness are lacking.

We have taken more time to discuss collagen-derived peptides because they are commonest ever found in the literature on FDPs portending RA management, however, other groups of FDPs like calcitonin exist. More studies using edge-cutting novel technologies

like computational modeling are warranted to decode the structure-activity of FDPs with regard to RA to establish perhaps personalized treatment options that ensure greater precision, accuracy, prediction, and efficacy. Finally, a robust approach involving human intervention studies is required to excavate the safety aspect of the studies. Taking these issues into consideration would support the comprehension of the modus operandi of FDPs and possible drug, functional food or nutraceutical product development that could effectively target and alleviate rheumatoid arthritis.

Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Chunhong Liu: Writing – original draft. **Zheng Yan:** Writing – original draft. **Xiaohai Zhang:** Writing – original draft. **Taibao Xia:** Writing – original draft. **Joseph O. Ashaolu:** Writing – original draft. **Opeyemi Joshua Olatunji:** Writing – original draft. **Tolulope Joshua Ashaolu:** Writing – review & editing, Writing – original draft, Visualization, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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