Review Article **Open Access**

Food bioactive compounds and the management of arthritis and its symptoms

Sydney Whited[1], Haruka Whitcroft[2], and Danik Martirosyan[3]

[1]Boston University, Boston, MA, 02215, USA; [2]University of Texas at San Antonio, San Antonio, TX, 78249, USA; [3]Functional Food Institute, San Diego, CA, 92116, USA

*Corresponding Author: Danik Martirosyan, PhD, Functional Food Institute, 4659 Texas Street, San Diego, CA, 92116, USA

Submission Date: June 19th, 2025; **Acceptance Date:** August 21st, 2025; **Publication Date:** August 25th, 2025

Please cite this article as: Whited S., Whitcroft H., Martirosyan D. Food bioactive compounds and the management of arthritis and its symptoms. *Agriculture and Food Bioactive Compounds* 2025; 2(8): 183 – 199.
DOI: https://doi.org/10.31989/AFBC.v2i8.1681

ABSTRACT

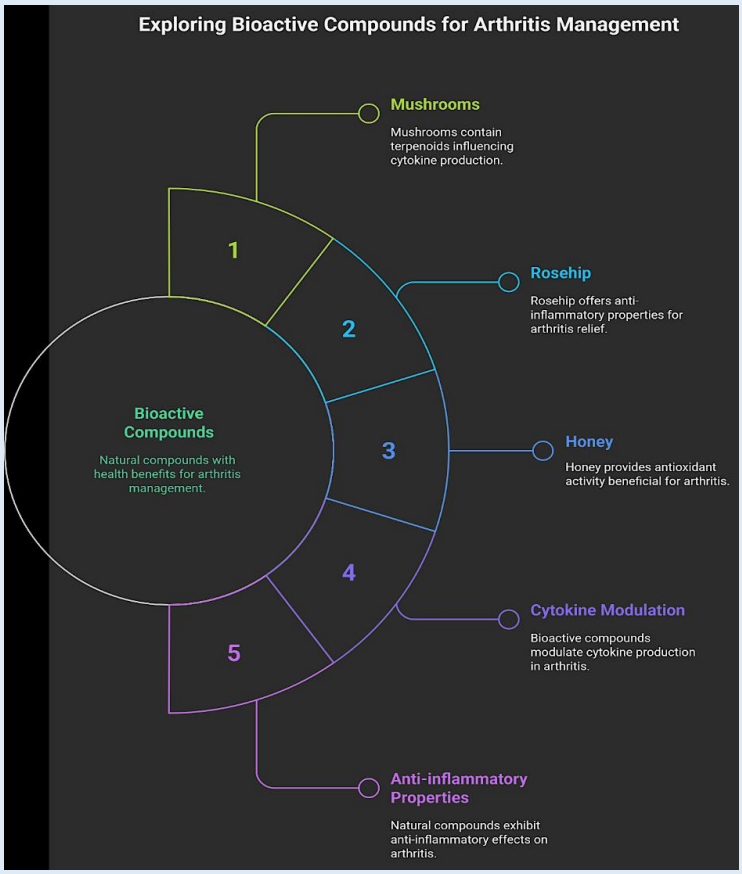
Bioactive compounds in food offer many health benefits, particularly to individuals with chronic inflammatory diseases. Among these compounds, terpenoids – commonly found in mushrooms – play a vital role in disease symptoms. Since mushrooms are commonly recognized for their terpenoid content, these compounds are known to influence cytokine production. Although these compounds are widely recognized for their therapeutic effects, studies often utilize rodent models rather than humans. In addition to mushrooms, other natural compounds in rosehip and honey offer similar anti-inflammatory properties. These data suggest that dietary patterns may affect disease outcome through the regulation of inflammatory messaging systems throughout the body. Further investigations are needed to understand how plant compounds in functional foods affect the human body. However, the safety of such compounds must also be evaluated since previous studies have shown gastrointestinal symptoms, altered mental status, seizures, and induced coma to occur when consumed at toxic doses. These items have not been established as functional foods due to inadequate research but may be recognized as such if they are able to follow a previously established certification pathway.

Novelty:

This research presents a comprehensive review of diverse food-derived bioactive compounds—focusing on terpenoids from mushrooms, bioactives from rosehip, and polyphenolic compounds in honey—and their role in managing arthritis and its symptoms. The study emphasizes not only their individual capacity to modulate cytokine production and attenuate systemic inflammation but also explores their synergistic and integrative potential when used in combination. By acting on key inflammatory pathways, such as cytokine signaling and oxidative stress modulation, these compounds

may offer complementary therapeutic benefits. While much of the current evidence relies on preclinical and animal studies, emerging data suggest promising clinical relevance, warranting further investigation in human trials. This review highlights critical research gaps, including the need for mechanistic studies on bioactive combinations and large-scale clinical trials to evaluate safety, efficacy, and interaction with standard therapies. Ultimately, the findings advocate for the strategic incorporation of these natural compounds into arthritis management, positioning them as cost-effective dietary interventions with the potential to improve patient outcomes."

Key Words: Rheumatoid Arthritis, Osteoarthritis, Gouty Arthritis, Terpenoid, Cytokine, Mushroom, Rosehip, Honey.



Graphical Abstract: Food Bioactive Compounds and the Management of Arthritis.

INTRODUCTION

Arthritis is a chronic disease characterized by systemic inflammation and progressive joint damage [1,2]. The progression of this condition is driven by cytokine networks that trigger synovial cell proliferation, ultimately damaging bones and cartilage [1]. A 2023 study found a significant correlation between cytokines such as IL-17 (interleukin-17) and arthritis [3]. Since cytokine production is linked to disease development, altering the production of these proteins may be a beneficial treatment technique. While the exact cause of RA remains unclear, its global incidence continues to rise each year [4,5].

Preclinical studies in rat models have demonstrated the therapeutic effects of mushroom consumption for inflammatory illnesses; however, human research is

limited [4]. Yet, dietary patterns are linked to arthritis symptoms, with both protective and harmful bioactive components in food products playing a vital role in disease pathogenesis [6,7]. For example, diets high in added sugars, saturated fat, and sodium disrupt the bacteria within the gut microbiome, directly worsening inflammation [8]. Chronic inflammation exacerbates arthritis symptoms, reinforcing the importance of diet quality in disease management [8].

Terpenoids found in various mushroom species can down-regulate cytokine systems within the body, which alter communication signals between cells, stimulating an immune response [6]. In addition to mushrooms, plant components such as beta-glucans decrease inflammation in the body by improving the immune system [9]. Furthermore, rosehip seed oil supports joint health through its high fatty acid and antioxidant content [10]. Honey, which is rich in flavonoid and phenolic content, offers notable antioxidant benefits [11].

Dietary Habits and Rheumatoid Arthritis: Many studies have concluded that the progression of Arthritis is linked to dietary patterns [6]. Nutrients such as polyunsaturated fats and antioxidants offer protective properties against the development of RA, while red meat advances the condition due to a high sodium content [6, 12]. These findings suggest that changes in the diet may lead to modifications of the gut microbiome, which influence disease outcomes [6]. Therefore, a diet rich in immunomodulatory compounds is encouraged [6].

Adopting a low-inflammatory diet that emphasizes the consumption of complex carbohydrates, fruits, vegetables, non-fat dairy, fish, white meat, legumes, and eggs is recommended [13]. In contrast, products high in salt and sugar should be limited due to their inflammatory properties [13]. With this, food products significantly affect those with arthritis-related conditions.

Food pyramid is a dietary guideline designed for RA patients provides recommended weekly portions for each food group. [13]. The food pyramid emphasizes plant-based diversity, with an increased consumption of fruits, vegetables, and spices [13]. This is recommended because varied gut microbiota have a positive effect on systemic inflammation [14]. Since gut microbiota differs between healthy and diseased individuals, there is a clear distinction between diet quality [14]. A diverse microbiota population promotes the fermentation of dietary fibers, which produce short-chain fatty acids that alter lipid metabolism and the body's immune response [8]. These metabolites modulate immune responses that may alleviate RA symptoms [15].

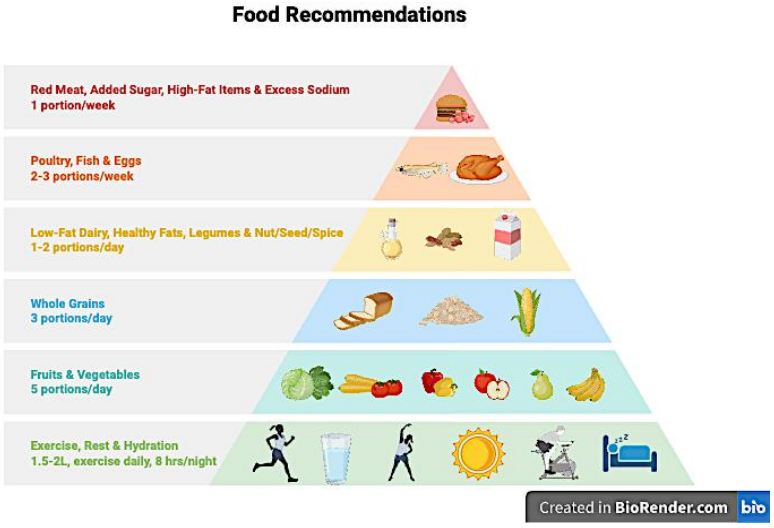


Figure 1: Food recommendations for individuals with arthritis

Figure 1 depicts the hierarchy of food groups and lifestyle patterns that have proven to prevent the onset of disease and alleviate inflammatory symptoms. Food recommendations are paired with exercise, rest, and hydration advice [16]. The association between dietary pattern and lifestyle choice shows a strong positive correlation, with increased levels of hydration, rest, and exercise alleviating risks and symptoms of poor health outcomes [17]. It is recommended that the diet is highly composed of fruits and vegetables, with the largest portion of the daily diet falling within this category. Foods high in saturated fats, added sugars, alcohol, and sodium should be limited due to their interaction with inflammatory signals that may worsen existing symptoms or increase one's risk of disease.

Food and Its Effect on Systemic Inflammation: Chronic low-grade inflammation contributes to the progression of non-communicable diseases, proven by recent human studies [18,19]. With a rise in these conditions, researchers have begun to evaluate food consumption – especially ultra-processed foods (UPFs) – as an associated lifestyle factor [18]. UPFS are often cheap, ready-to-eat, and delicious, making them appealing to many individuals [18]. However, studies have found that the consumption of UPFs is associated with the progression of chronic diseases due to their composition of dietary components [18]. These components affect the gut microbiota, leading to systemic changes in inflammation [18].

Ingredients such as saturated fats, sodium, and added sugars contribute to inflammation within the body, which may have adverse health effects. Since these foods dictate the gut microbiome, inflammation can worsen over time with continuous over-consumption [8].

Beyond physical health, UPFs are associated with depression through their interaction with the amygdala-hippocampal complex [20]. Excess UPF consumption is linked to depressive symptoms in every participant evaluated during a 2023 study [20]. Furthermore, a stronger association was observed in individuals with obesity or altered white blood cell counts [20]. This association may be mediated by the gut-brain axis, with a reduced microbial diversity [8]. Overall, excess consumption of UPFs negatively impacts human health, highlighting the importance of nutrient-rich diets to manage inflammatory conditions [21].

Dietary Patterns to Advance RA: Diets high in sugar have been linked to the progression of RA [22]. Interestingly, a 2023 study found that the risk of death due to diet quality from CVD or stroke was not significantly higher among individuals diagnosed with RA [23]. This suggests that RA itself contributes to mortality risk regardless of dietary pattern [23]. Despite this, physical activity and diet are positively correlated to the improvement of RA symptoms [24].

Environmental factors play a large role in rheumatic and musculoskeletal diseases due to their influence on systemic inflammation [11]. Some evidence suggests that diet is a protective factor against the onset of RA [4]. However, more extensive research must be conducted to conclude an association between diet composition and inflammatory symptoms and disease development.

Among many dietary approaches, the Mediterranean diet has proven to decrease pain levels in individuals diagnosed with RA [25]. The high content of omega-3's within this diet contribute to the management and treatment of inflammatory conditions [26]. This emphasizes the significance of nutrition therapy for individuals with arthritis-related conditions.

Diet and weight management are essential to maintain healthy lifestyles [6]. Notably, the inclusion of spices, antioxidants, and probiotics is linked to symptom relief [27]. Moreover, anti-inflammatory diets aim to reduce pain levels, while other dietary approaches do not [28].

Worsening symptoms are due, in part, to an altered gut microbiota composition in RA patients [29]. The Mediterranean diet modulates the gut microbiota and

intestinal barrier through its high polyunsaturated fatty acid content, offering promising therapeutic effects [30].

Given the association between poor diet quality and increased pain levels, disease activity in terms of diet composition is necessary to evaluate for disease management [31].

Terpenoids and Their Properties: Terpenoids are organic compounds found in mushrooms that have anti-inflammatory properties [32]. *Ganoderma lucidum* (Reishi), for example, has been used as an anticancer, antitumor, and antioxidant remedy, as it is high in flavonoids and polysaccharides [4]. These terpenoids have been found to modulate cytokine production and prevent oxidative stress damage within the body [4]. Therefore, mushrooms have a promising influence in the management of inflammatory conditions such as Rheumatoid Arthritis (RA), Gouty Arthritis (GA), and Osteoarthritis (OA) [33][34].

Terpenoids have synergistic properties, as the bioavailability and therapeutic properties can increase with many varieties consumed at once [33]. The increased efficacy of these bioactive molecules are of a vast economic value. However, the production of terpenoids remains difficult as many methods have low yields, low purity scores, and it is nearly impossible to keep all batches uniform [35]. Previous methods include maceration, solvent extraction, and hydrodistillation [35]. New strategies including pressurized liquid extraction (PLE), static headspace (HS) extraction, microwave associated hydrodistillation (MAHD) and supercritical fluid extraction (SFE) use less solvent volumes to alleviate environmental harm, while lowering extraction time for a given terpene [35]. However, each terpenoid may require different extraction methods. Further research is needed to understand efficient extraction methods that could allow pharmaceutical companies and medical professionals to use these bioactive components safely and more readily [37].

Mushroom Components That May Reduce Inflammation: The health benefits of mushrooms have gained attention in the nutrition and health field. A 2022 study by Sun et al. demonstrated that mushrooms such as *Sanghuangporus vaninii* (SV) and *Inonotus hispidus* (IH) reduce inflammatory cell swelling, demonstrating their potential benefit in managing GA symptoms [37]. Similarly, He et al. (2016) observed that RA patients consumed fewer mushrooms than the healthy controls within the study, indicating a potential dietary influence in the progression of RA. Since mushrooms have high contents of beta-glucans, polysaccharopeptides, and polysaccharide-protein conjugates, which are known to be immunomodulatory, they could help reduce inflammation. Beta-glucans are known to stimulate an anti-bacterial immune response, which is partnered with stronger immune defenses within the body [38]. Furthermore, beta-glucans directly enhance immunity within the digestive tract, which lowers inflammation through a strengthened digestive system that protects the body from foreign entities [38].

Mechanism of Beta-Glucans: The structure of beta-glucans allows this compound to modulate the immune system. Beta-glucans are able to promote dendritic cell maturation, cytokine secretion, and regulate glucan receptors. These components are found in double helix, single helix, or random helix forms. The three structures are able to transform into each other, which allow for proper ligand-receptor interactions [38]. The branches and length of these structures allow them to bind to receptors, which provide the immunomodulatory effects [38]. As beta-glucans from different species differ in structure, their binding affinity to cells also differs [38]. Although this mechanism is not fully understood, there is concluded to be a strong association between the structure of beta-glucans and its ability to modulate immune responses within the body [38].

Cytokine Systems: Beta-glucans are able to stimulate the production of cytokines, through the activation of the immune system. . Environmental factors are known to play a significant role in the development of rheumatoid arthritis, making it essential to understand the regulation of cytokine systems. Recent research suggests that certain natural compounds, such as those derived from medicinal mushrooms, may help modulate these cytokine responses and potentially support the management of inflammatory conditions like rheumatoid arthritis [53]. Cytokines work in conjunction with other immunomodulatory proteins and hormones to send messages between cells that determine the body's immune reaction [39]. Therefore, the down-regulation of cytokines could offer therapeutic benefits for OA. Ramya et al. (2022) found that wild, edible mushrooms are arthritis edema-inhibiting, as well as free radical scavengers [40]. Similarly, Wu et al. (2022) found that Ganoderma mushrooms could be used to treat RA [41]. The association between Ganodermic acid A (GAA), extracted from the mushroom, and the treatment of OA symptoms were studied to conclude that GAA down-regulates the expression of osteoprotegerin (OPG) and up-regulates the expression of nuclear factor kappa-B ligands (RANKL) within human chondrocyte cells with a diminished matrix metallopeptidase secretion in synovial fluid [41]. Therefore, Ganoderma mushrooms could improve OA symptoms by influencing the RANKL and OPG ratio within the body, decreasing the secretion of the MMP-13 enzyme that propels cartilage degeneration in OA [41].

Research has concluded that White Button Mushrooms (WBM) may be beneficial in the management of inflammatory diseases by reducing cytokine production through terpenoid interactions [42].The bioactive compounds in mushrooms offer therapeutic benefits for Arthritis patients, leading researchers to the hypothesis that mushrooms could play a protective role in inflammatory disease pathogenesis and management [32][.

A study using the *Antrodia camphorata* species found that the bioactive components of antcins and antroquinonol are constituent to the *Antrodia camphorata* plant [43].These terpenoids have anti-inflammatory, neuroprotective, and antidiabetic properties that could help alleviate various arthritis symptoms [44]. Similarly, there are 108 terpenoids found in Chaga, some of which are steroids [45]. Methanol and ethanol extracts of Chaga have been concluded to inhibit macrophage activity, which reduces cytokine production and leads to less inflammation within the body [45].

Clinical Evidence: Many studies work in conjunction to support the hypothesis that the terpenoids in mushrooms could play a protective role in inflammatory disease pathogenesis and management [46]. However, additional human clinical studies would be needed to further research the effect of terpenoid content in mushrooms, and the pathogenesis of arthritis. Other dietary components have been previously evaluated for their anti-inflammatory properties that could serve as treatment options for individuals who suffer from RA.

Research has found a strong association between low-fat and low-sodium diets, physical activity, proper hygiene, sleep, and smoking and RA symptoms [47]. Lifestyle modifications that lead to an adequate macronutrient intake has shown to vastly improve OA symptoms, while also improving bone and cartilage mineralization [48]. This is further concluded in a 2022 study that emphasizes that diary components play a role in the progression of musculoskeletal diseases and related conditions [49].

Table 1. Functionality and benefits of mushrooms and bioactive mushroom compounds

Functionality & Benefits	Food or Plant Component	Reference
Reduce inflammatory cell swelling	Mushrooms: *Sanghuangporus vaninii* (SV) and *Inonotus hispidus* (IH)	[37]
Anticancer, antitumor, and Antioxidant properties	*Ganoderma lucidum* (Reishi) high in flavonoids and polysaccharides	[4][50][51]
Arthritis edema-inhibiting & free-radical scavengers	Edible mushrooms	[40]
These terpenoids have anti-inflammatory, neuroprotective, and antidiabetic properties that may alleviate Arthritis symptoms	*Antrodia camphorata* plant (medical mushroom of Taiwan)	[52]
Stimulate anti-bacterial immune response	Beta-glucans	[9]
down-regulate cytokine systems Cytokines work with immunomodulatory proteins/hormones to determine the body's immune reaction	*Hericium erinaceus* (Lion's Mane)	[53]
Ganodermic acid A (GAA), can be extracted from the mushroom GAA down-regulates the expression of osteoprotegerin (OPG) and up-regulates the expression of nuclear factor kappa-B ligands (RANKL) within human chondrocyte cells with a diminished matrix metallopeptidase secretion in synovial fluid	Ganoderma mushrooms	[41]

Data in Table 1 shows that bioactive compounds in mushrooms, such as Beta-glucans, Ganodermic acid A, flavonoids, and polysaccharides, have antioxidant, neuroprotective, and anti-inflammatory properties. These components can stimulate an antibacterial immune response while down-regulating cytokine systems within the body. Adherence to diets heavily composed of these compounds may alleviate arthritis-related symptoms.

Rosehip's Anti-Inflammatory Properties: Rosehip can be used as a medicinal plant from the Rosacease family [54]. They are historically known for their high vitamin C content, with up to 473% of one's daily value in 100 g [55]. Not only does rosehip offer immune support, but it also promotes the production of collagen [55]. For these reasons, rosehip may be helpful for individuals with arthritis through its ability to reduce pain and stiffness in the body due to inflammation [56]. Through its vast vitamin and mineral composition, this product offers promising treatment and management options to individuals who struggle with systemic inflammation or RA-related conditions.

In vitro, in vivo, and clinical trials have found that rosehip fruits without seeds could be used to treat poor joint health through an excess of anti-inflammatory properties that could support joint health [10]. Compounds can be isolated from this product and used for other goods such as oils [10]. The benefits of rosehip stem from its anti-inflammatory properties that inhibit proinflammatory enzymes, decrease cytokine levels in the body, and lower C reactive proteins [10][57]. Galactolipids isolated from rosehip seeds have improved the quality of life for Osteoarthritis patients when studied under in vitro settings [10].

A 2023 study used ten samples of *Rosa canina L.* and *Rosa rubiginosa L.* from Southern Chile to evaluate crude proteins, minerals, phenolic compounds, and antioxidant levels in the samples [58][59]. The analysis concluded high levels of ascorbic acid, flavonols, and antioxidants within the samples evaluated [58].The highest antioxidant levels were attributed to that of *the Rosa rubiginosa L.* samples [58]. This study was conducted in order to determine the strength of this good as functional food, with the intention of developing new treatment or prevention strategies for diseases that increase inflammation in the body [58].

Rosehip seeds are also valuable once the extract is obtained. The defatted seeds of *Rosa Rugosa* contain dietary fibers, protein, minerals, polyphenols, and antioxidants [60].The seeds are composed of about 65% dietary fibers, 15% protein, and .4% fat. When the seeds are defatted with CO2, they contain about half the energy content of other seed varieties due to their low-fat content [60]. Examples of antioxidants observed in such species are flavanols (.9%) and total ellagic acid (.5%). Flavonoids modulate cellular enzyme function, which influences the production of COX, an endogenous enzyme that is able to synthesize prostaglandins to initiate pain or inflammation [61]. Such values display the overarching benefits of the whole seed.

Table 2. The benefits of rosehip classified by species type

Benefits:	Species:	Reference:
Antioxidant and antimicrobial	*R. canina*	[62]
Source of phytochemicals	*Rosa canina L.*	[60]
High Vitamin C content Collagen production	*Rosa (all)*	[55]
Highest amount of polyunsaturated fatty acids (linoleic acid and alpha-linoleic acid) Great source of polyphenol High in prostaglandins and nitric oxide → reduce secretion of various cytokines	*Rosa (all)*	[63]
Flavonoid intake is associated with decreased oxidative damage and chronic inflammation → Rosehip's diverse bioactive profile could allow for RA treatment	*Rosa canina L.*	[60]
Phenolic acids: oleanolic, betulinic, citric, ursolic, cinnamic, caffeic, and ferulic acids	*Rosa canina L.*	[60]
Flavonoids: quercetin, rutin, ellagic acid content	*Rosa canina*	[60]
carotenoids: chlorophyll and lycopene, proanthocyanidins → antioxidant parties and protect cells from oxidative damage	*Rosa canina*	[60]
Defatted seeds through the use of CO2 contain dietary fiber, protein, minerals, and antioxidants There is a benefit to rosehip beside essential oil content	*Rosa Rugosa*	[60]
High polyphenol and vitamin C content Anti- inflammatory, antioxidant, and anti-obesogenic activities wide range of bioactive compounds including the anti-inflammatory galactolipid:(2S)-1,2-di-O-[(9Z,12Z,15)-octadeca-9,12,15-trienoyl]-3-O-β-D-galactopyranosyl glycerol (GOPO), vitamin C, phenolics, lycopene, lutein, zeaxanthin, and other carotenoids	*Rosa canina L.*	[64]
Counter lipid peroxidation, oxidative stress, inflammation Vitamin C also found within the product	*Rosa canina L.*	[57]
high levels of fatty acids and antioxidants Galactolipids Joint health → anti-inflammatory properties inhibit proinflammatory enzymes, decrease cytokine levels, lower C reactive proteins	Rosehip seed oil	[10]

Table 2 displays the bioactive compounds found in rosehips, which have anti-inflammatory, antioxidant, and anti-obesogenic activities and contribute to their vast array of positive effects. Among these known bioactive compounds, strong anti-inflammatory and antioxidant effects have been correlated to vitamin C, phenolics, lycopene, lutein, zeaxanthin, and other carotenoids.

Table 3. The benefits of vitamins and minerals found in rosehip

Vitamin/Mineral	Benefit	Reference
Vitamin C	Promote immune system	[65][66]
Vitamin C	Antioxidant Cofactor for collagen biosynthesis	[65]

Vitamin/Mineral	Benefit	Reference
Vitamin C	Counter inflammation through preserved content in *Rosa canina L.* Could treat glomerulonephritis	[57]
Vitamin C	Anti- inflammatory, antioxidant, and anti-obesogenic activities	[64]
Vitamin E	Protect cells from free radicals	[55]
Vitamin K	Bone health 199.2 mg/100 g in defatted seeds	[55] [60]
Vitamin A	Immune function Anti-inflammatory Bone health	[60]
Ca, Mg, Na, Mn	Ca: 175.9 mg/100 g Necessary to prevent osteoporosis – arthritis patients can be vulnerable to bone loss due to lifestyle modifications at onset of disease Mg: 83.9 mg/100 g Plays a role in homeostasis and energy balance – determines cell fate which can influence the microbiome and inflammatory responses within the body Na: 3.5 mg/100 g (low content) Excessive salt intake can worsen arthritis symptoms Mn: Bone health and connective tissue maintenance	[60] [67] [60] [44] [60] [35] [55]

Table 3 demonstrates the antioxidant effects of vitamin C, but also of vitamin E, vitamin A, and vitamin K. These vitamins and minerals can contribute to the anti-inflammatory benefits of rosehip compounds, while supporting immune function.

Honey and its Anti-Inflammatory Properties: Honey, produced by honeybees and stingless bees, varies in composition of flavonoid and phenolic compounds [68]. Recent studies have shown that the bioactive components in honey contain anti-inflammatory properties that could be linked to prevent inflammatory diseases such as arthritis and diabetes [68]. As honey has readily bioactive polyphenolic compounds, ingestion of foods containing this priority may target inflammatory pathways that affect RA patients [68]. In a 2023 study evaluating the effects of diet and joint symptoms, researchers concluded that diet plays a distinct effect in inflammatory symptoms [69]. Among participants, many reported that honey reduced joint pain [69].

Other studies have found the promising effects of bee venom therapy, which offers therapeutic effects for individuals who suffer from RA [70]. Bee venom contains peptides, enzymes, amines and nonpeptide components that target inflammation within the body, leading to the alleviation of inflammatory-related symptoms [70]. Although this therapy is commonly used, some experience adverse effects such as swelling or excessive itching [70]. Further data must be evaluated to conclude the efficacy of this therapeutic method in the treatment or RA.

Honey aids arthritis symptoms due to its high content of polysaccharides and polyphenols that influence immunomodulatory factors [68][71]. Honey provides a promising approach to disease management through its ability to inhibit proinflammatory enzymes and cytokine production [72][73].The proteins found in Ziziphus honey can down-regulate inflammatory markers such as TNF-α, IL-1β, IFN-γ, iNOS, caspase 1, Calgranulin A (S100A8) and NF-κB expression, providing anti-inflammatory effects [74]. *Lespedeza bicolor* Turcz. (*L. bicolor*) honey is able to inhibit ferroptosis, which is cell death through the accumulation of iron-dependent lipid peroxidation, through the activation of various inflammatory pathways [75][76]. Honey can also reduce the circulation of Interleukin-6 (IL-6), which modulates cytokine production [77]. These findings offer pain suppression effects that can also influence healthy aging through the reduction of oxidative stress[78]. Moreover, food plays a key role in disease management and

prevention through the modulation of inflammatory factors that may reduce joint pain [79].

Limitations and Opposing Data: Some studies have reported that extracts of the family of Basidiomycota-white-rot fungi – specifically Lentinula edodes, Agaricus bisporus, Pleurotus ostreatus, Pleurotus columbinus, and Pleurotus sajor-caju – exert immunostimulatory effects on rat models [80]. These immunomodulatory effects were noticed when higher doses of extracts were administered, which may be considered as an effective therapeutic dose. The effective therapeutic dose of edible mushroom extracts improved immune function. Although an effective dose was found, there are potential concerns for Arthritis patients. Since mushroom extracts increase immune activity, excess damage and inflammation may worsen in Arthritis patients. More research must be done to determine if the pathology in rat models is similar to that of human subjects, to confirm this concern.

Moreover, not all studies have found significant associations between anti-inflammatory diets and improved Arthritis symptoms . Confounding factors such as genetics likely play a crucial role in the progression of this condition. Further, environmental factors have proven to affect RA [81]. However, a more in-depth study analysis must be conducted in order to eliminate counting variables that alter the association between diet and health outcome. Modifiable risk factors for the disease must be evaluated through clinical trials to understand the true association between dietary pattern and RA symptoms [81].

Although research has shown the positive effect of rosehip extract, studies conducted have included limited human samples, lack major statistical power, and have only shown a modest effect size (Australian Family Physician). Therefore, further research must be conducted to evaluate the true efficacy of the product for arthritis patients.

Honey has provided promising results through its rich nutrient content and high antioxidant activity [82][83]. However, results from in vitro and in vivo studies fail to prove the metabolic pathways that honey acts upon [82]. Therefore, further research must be conducted to evaluate the effectiveness of honey against inflammatory conditions such as arthritis [82].

CONCLUSION

The novelty of this research lies in its innovative approach to holistic health and healing for Arthritis and its related diseases. As there is no uniform treatment for Arthritis patients, the strongest remedy remains unclear [84-86].

With an increasing prevalence due to modern environmental causes, food could serve as a protective factor against such diseases [17] [87-89]. Increasing mushroom consumption may provide a cost-effective method to alleviate symptoms. Further research may provide new remedies that utilize mushroom extracts and bioactive plant components that provide anti-inflammatory effects.

Although much of the research discussed in this review has been conducted on animal models, more data must be collected using human samples to understand the complexity and integration of these ingredients. Human studies are difficult to conduct due to ethical protocols and the strength of current evidence.

In Japan, several commercially available bioactive supplements are widely used by patients with rheumatoid arthritis (RA). Recent surveys have reported that 46% of RA patients experience beneficial effects from dietary supplements, including relief from common symptoms such as joint pain, swelling, stiffness, and fatigue [90]. Frequently used supplement ingredients include marine oil (fish oil), glucosamine—a compound found in cartilage that may help maintain joint health—vinegar, and chondroitin. Chondroitin (often seen as chondroitin sulfate) is a natural component of cartilage, the firm connective tissue that cushions joints, and is

thought to help retain moisture within joints, reduce inflammation, and slow the breakdown of cartilage.

Although the definition and range of supplements may vary, polyunsaturated fatty acids (PUFAs) emerged as the most commonly consumed bioactive compounds. Among these, docosahexaenoic acid (DHA; 22:6 ω-3) and eicosapentaenoic acid (EPA; 20:5 ω-3) were especially popular, indicating a preference for ω-3 fatty acids to support joint health. Reported clinical benefits of PUFAs or fish oil in RA include reducing the number of swollen joints, improving morning stiffness [91], lowering dependence on non-steroidal anti-inflammatory drugs (NSAIDs) [92], and decreasing overall disease activity scores (DAS) [93].

When integrating bioactive food compounds or supplements into RA treatment strategies—either as complementary options or alternatives—potential interactions with standard medications must be carefully evaluated. For instance, folic acid supplementation is routinely recommended for patients undergoing low-dose methotrexate (MTX) therapy, a commonly prescribed drug for RA. MTX can interfere with folate metabolism, leading to adverse effects such as mouth sores, liver dysfunction, and gastrointestinal upset. Although concerns have been raised about whether folic acid might reduce MTX's effectiveness or increase cancer risk, current evidence in RA populations does not support these concerns. On the contrary, studies show that folic acid supplementation significantly reduces side effects without compromising the therapeutic benefit of MTX, making it a well-established and valuable practice in clinical settings [94].

Nevertheless, it is essential that the use of folic acid and other bioactive compounds be continuously re-evaluated through ongoing clinical trials and systematic reviews of both domestic and international literature. This will help to better understand which dietary supplements or bioactive food ingredients may interact positively—or negatively—with medications used in the management of rheumatoid arthritis.

Developing functional food products for the management of arthritis and its symptoms is a promising strategy that capitalizes on the synergistic effects of bioactive compounds from natural sources. Functional foods, as conceptualized by the Functional Food Center (FFC), are defined as food or food components that provide health benefits beyond basic nutrition, including the prevention and treatment of diseases .[95][96]. This definition underpins the approach to designing products that can directly influence the underlying pathologies of arthritic conditions, primarily through anti-inflammatory, antioxidant, and immunomodulatory actions [95][97].

The development of such products typically follows a structured process. It begins with the identification and selection of bioactive compounds with documented efficacy against arthritis-related inflammation and oxidative stress. This often involves screening diverse sources like fruits, vegetables, herbs, and certain animal-derived ingredients for specific compounds such as polyphenols, flavonoids, and omega-3 fatty acids, known for their ability to inhibit pro-inflammatory cytokines and modulate oxidative pathways [97-99]. Subsequently, the formulation phase focuses on combining these selected ingredients to achieve enhanced bioavailability and synergistic benefits, acknowledging that multi-component interactions can yield greater therapeutic effects than individual compounds]. [96][100]

Further steps involve rigorous product design and testing. This includes ensuring the stability of bioactive compounds throughout processing, packaging, and storage to maintain their therapeutic potency. Comprehensive in vitro, in vivo, and ultimately human clinical trials are essential to validate the efficacy, safety, and optimal dosage of the functional food product for arthritis management .[95][101] Finally, considerations for palatability and consumer acceptance are paramount

to ensure that these products are not only effective but also convenient and enjoyable for regular consumption, thereby promoting adherence and long-term benefits for individuals managing arthritis and its symptoms [96]. This systematic approach aims to translate scientific understanding into accessible dietary interventions.

In summary, Mushrooms, rosehip, and honey contain bioactive compounds with functional properties that offer significant health benefits. These natural products demonstrate immunomodulatory activity by influencing cytokine production and reducing systemic inflammation. The evidence reviewed in this article supports the potential of these substances in the prevention and management of arthritis. However, further clinical research is necessary to confirm their efficacy and formally classify them as functional foods that can prevent or manage Arthritis. These findings have broad implications—not only in pharmaceutical and medical fields but also in environmental, cosmetic, and chemical industries. Given their therapeutic potential and accessibility, these products hold promising economic and health value for future development and application.

List of Abbreviations: RA: Rheumatoid Arthritis; OA: Osteoarthritis; GA: Gouty Arthritis, IH: *Inonotus hispidus;* SV: *Sanghuangporus vaninii;* RANKL: Nuclear Factor Kappa-B Ligands; OPG: Osteoprotegerin**;** GAA Ganodermic Acid A; SFE: Supercritical Fluid Extraction; PLE: Pressurized Liquid Extraction; HS: Static Headspace; MAHD: Microwave Associated Hydrodistillation; WBM: White Button Mushrooms; FFP: Functional Food Product; BC: Bioactive Compound

Competing Interests: The authors have no financial interests or conflicts of interest.

Author's contributions: DM: conceptualization, supervision, review, writing; SW: writing, editing, proofreading; HW: critical review, writing, formatting.

Acknowledgements: No external funding was needed or given for this review article

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