Review

The Role of Dietary Phenolic Compounds in the Prevention and Treatment of Rheumatoid Arthritis: Current Reports

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Posted Date: 8 April 2024

doi: 10.20944/preprints202404.0585.v1

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The Role of Dietary Phenolic Compounds in the Prevention and Treatment of Rheumatoid Arthritis: Current Reports

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Abstract: Rheumatoid arthritis (RA) is a complex illness with both hereditary and environmental components. Globally, in 2019, 18 million people had RA. RA is characterised by persistent inflammation of the synovial membrane that lines the joints, cartilage loss, and bone erosion. Phenolic molecules are the most prevalent secondary metabolites in plants, with a diverse spectrum of biological actions that benefit functional meals and nutraceuticals. These compounds have received a lot of attention recently because they have antioxidant, anti-inflammatory, immunomodulatory, and anti-rheumatoid activity by modulating tumour necrosis factor, mitogen-activated protein kinase, nuclear factor kappa-light-chain-enhancer of activated B cells, and c-Jun N-terminal kinases, as well as other preventative properties. This article discusses dietary polyphenols, their pharmacological properties, and innovative delivery technologies for the treatment of RA, with a focus on their possible biological activities. Nonetheless, commercialization of polyphenols may be achievable only after confirming their safety profile and completing successful clinical trials.

Keywords: Anti-inflammatory activity; phenolic compounds; rheumatoid arthritis; diet; quality of life

1. Introduction

There exist more than 100 conditions of arthritis known, and amongst them, rheumatoid arthritis (RA) is one of the most common forms observed in elderly population [1]. RA affects 0.1–2.0% of the population worldwide, being three-times more common in the female gender. The condition can begin at any age, although around 80% of all individuals begin the disease between the 35 and 50 years old. Their etiology remains poorly understood, and despite recent therapeutic advances, there is no known cure [2].

RA is a systemic autoimmune, chronic, heterogeneous, and inflammatory disease in which your immune system mistakenly attacks healthy cells in the body, reducing quality of life and shortening its duration [3,4]. RA is a complex process involving numerous inflammatory mediators, and is characterized primarily by aggressive synovial hyperplasia, synovitis, progressive cartilage degeneration, and bone erosion with painful swelling of small joints, fatigue, prolonged stiffness, and fever produced by immune responses and particular innate inflammatory processes [4,5]. Although RA affects multiple body systems, the joints of hands, wrists, feet, ankles, knees, shoulders and elbows are most often affected [6]. The lining of the joint becomes inflamed in RA joints, causing joint tissue destruction. Long-term or chronic discomfort, unsteadiness (loss of balance), and deformity

 doi:10.20944/preprints202404.0585.v1

(misshapenness) can result from this tissue injury. RA can also affect other tissues and organs, including the lungs, heart, and eyes [1,7].

Although RA changes have been extensively investigated, there is a still lack of effective drugs. During RA, there are many pro-inflammatory cytokines, such as interleukin (IL)-1, IL-6, IL-17 and TNF-α, and chemokines released to the synovial space [4]. Therefore, it is urgent to find effective drugs for RA by inhibiting the production and release of pro-inflammatory cytokines. Until date, non-steroidal anti-inflammatory agents and disease-modifying anti-rheumatic drugs, like immunosuppressants and monoclonal antibodies (e.g., rituximab and tocilizumab) combined with methotrexate, are largely used to attenuate RA; however, most of them are expensive, rarely effective and tolerable and lead to several unwanted effects, including allergy and infections, gastrointestinal problems, fluid retention, renal dysfunction and systemic vasculitis, cytopenia, lymphopenia, neutropenia and the elevation of transaminase and cholesterol [7–13]. Among the new and most promising availability strategies, special attention has been given to bioactive molecules largely found in nature, namely polyphenolics, since their chemical structure with catechol methoxy and pyrogallol groups, confers them notable health benefits, like antioxidant, anti-inflammatory and antiproliferative activities, as well as capacity to prevent neurological and cardiovascular pathologies, without, it is believed, side-effects [14–21]. In addition, polyphenolics are also easier to obtain, water-soluble and more economical than chemical drugs, and have already shown effectiveness in inhibiting JAK proteins and JAK/STAT signalling pathways [22–26]. Particularly, curcumin displayed capability to relieve the rheumatoid arthritis progression by suppressing the inflammatory responses, synovial hyperplasia and protein expression levels of phosphorylated JAK2 and STAT3 in mice with collagen-induced arthritis model that were treated at a dose of 100 μM curcumin/day for almost three months [27], while, by docking studies, salvianolic acid C exhibited a great affinity binding for JAK (10.7 kcal/mol) [22]. In addition, phenolic-rich extracts of sweet cherries have already displayed a notable ability to scavenge cellular nitric oxide species and diminish inducible nitric oxide synthase (iNOS) and cyclooxygenase (COX)-2 expression [28].

Keeping these facts in mind, the main goal of this work is to review and discuss the dietary polyphenolics commonly found in diet and their rich sources in preventing and/ or attenuating RA, the most advanced strategies and also suggest future search.

2. Data Collection

The data collection was searched from the time of their establishment to March 24th, 2024, through the scientific databases National Center for Biotechnology Information (NCBI), Google Scholar, PubMed, ResearchGate, Science Direct, Scopus, SpringerLink, Web of Science, and trusted abstracts. The free terms, keywords, or MeSH terms used were polyphenols, phenolics, total phenolics content, phenolic-rich sources, antioxidant effects, anti-inflammatory properties, health benefits and rheumatoid arthritis combined with AND, OR, or NOT operators. During the literature review, there were no restrictions on the author(s) or type of publication. In the final, 325 papers were cited in this review.

3. Major Sources of Dietary Polyphenols

Nowadays, the search for more effective, safer and cheaper bioactive compounds than chemical drugs assume great importance. Indeed, and once most chemical drugs possess several unwanted effects and are little active, many people prefer to use natural molecules [29]. Among the most promising molecules, phenolic compounds, including simple phenols (e.g., catechol, phenol, phloroglucinol and resorcinol) and polyphenolics (e.g., coumarins, anthocyanins, lignans and phenolic acids) seem to be promising therapeutic and/or adjuvant approaches (Figure 1) [30–32]. Simple phenolics present a low molecular weight, being rapidly absorbed by human skin, while polyphenolics are largely widespread and ubiquitous in nature, being largely found in several algae, beans, fruits, barks, herbs and spices, legumes, leaves, nuts, whole grains, oilseeds and roots (Table 1) [33,34].

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In a general way, stilbenes are predominant in grapevines, peanuts and sorghums (amounts of 0.16-0.77 mg per 100 g, 1.8-787.3 μg per 100 g and up 0.01 mg per 100 g, respectively), showing total polyphenol compounds (TPC) of 9.3-75.3, 94.4-228.4 and 100-2300 mg GAE per 100 g fresh weight (fw), respectively [35–38]. Lignans are highly present in flaxseeds (amounts of 9 to 30 mg per g, being 75 to 800 times higher than in cereals, fruits, legumes and vegetables), revealing TPC scores around 3000 mg per 100 g [39,40]; in addition, flaxseeds also present considerable quantities of phenolic acids (800-1000 mg per 100 g) [41].

Focusing on phenolic acids, namely the hydroxybenzoic ones, they are mainly found in black radish, onions, oak bark, and tea, gall nuts, sumac, grapes and wine, while hydroxycinnamic acids are largely present in fruits, vegetables and coffee [42–45].

Focusing on anthocyanins, they are widely found in red and purple fruits and vegetables, being inclusive considered the main responsible for their vibrant colours and health-promoting properties exhibited by them. Specifically, cyanidin 3-*O*-rutinoside is mainly found in sweet cherries, while cyanidin 3-*O*-glucosyl-rutinoside is the predominant anthocyanin in sour cherries [46,47]. Regarding TPC values, sour cherries present higher values than the sweet ones [275.3-652.27 against 72.9-493.6 mg gallic acid equivalents (GAE) per 100 g fw for sweet cherries] [47–49]. On the other hand, the TPC of blueberries fluctuates between 2.7 and 585.3 mg GAE per 100 g fw, being richer in peonidin derivatives, whereas for black elderberries, TPC is around 537.9 mg GAE per 100 g fw and cyanidin 3-*O*-sambubioside is the main anthocyanin [50–53]. Blackberries also present considerable amounts of TPC (292.2-446.4 mg GAE per 100 g fw), being cyanidin 3-glucoside, the major anthocyanin [54,55]. For strawberries, TPC varies from 36.5 to 116.3 mg GAE per 100 g fw, being the most abundant, pelargonidin 3-*O*-glucoside [56–58], while for grapevines (TPC 9.3-75.3 mg per 100 g fw), malvidin 3-*O*-glucoside is the predominant anthocyanin [38,59,60]. Additionally, mulberries and chokeberries also present considerable amounts of TPC (424-485 and 1022.4-1705.9 mg GAE per 100 g fw, respectively), being cyanidin 3-sophoroside and cyanidin 3-*O*-galactoside, the predominant ones, respectively [61-63], whereas black currants are richer in delphinidin 3-rutinoside and present TPC values fluctuating from 1930.0 to 3410.0 mg GAE per 100 g fw [64,65]. Red cabbage also presents considerable TPC scores (115.31 mg per 100 g fw), being the most prevalent anthocyanin, cyanidin 3-*O*-diglucoside-5-*O*-glucoside [66,67].

Isoflavones (e.g., genistein and daidzein) are abundant in soybeans (total isoflavones and TPC values of 80.7-213.6 mg per 100 g, and 87.2-216.3 mg per 100 g fw, respectively); within isoflavones, genistein is the most found, followed by daidzein (21.4-78.3 and 15.0-67.4 mg per 100 g, respectively) [68]. Regarding coumarins, marmelosin is highly found in Aegle quince fruits (290 g per 100 g, for TPC values varying from 905.0 to 4900.0 mg GAE per 100 g) [69,70].

Regarding flavan-3-ols, the presence of (+)-catechin was reported in peaches, apricots, apples and green tea, whereas (-)-epicatechin in apricots, sour cherries, apples, cholate, cocoa and green and black tea [71–73], and epigallocatechin gallate, in green tea [74]. Flavonols, specially kaempferol, are largely present in leaves, papaya shoots, pumpkins, carrots and black tea [75,76], while *Mentha pulegium* L. is rich in quercetin [77], whortleberries, lingonberries, chokeberries and cranberries, in myricetin, and strawberries, apples, persimmons, grapes, onions, and cucumbers, in fisetin [78]. Relatively to flavanones' compounds, higher levels of hesperetin and naringin are found in citrus fruits [79], except eriodictyol is present in Yerba Santa [80]. Regarding flavonones, hesperidin derivatives are also predominant in citrus fruits [81], while honey and propolis present higher levels of pinocembrin [82], and *Glycyrrhiza Glabra* L. plant parts are rich in liquiritin [83].

Of course, quantity values are greatly influenced by genotype, origin, climate, time of harvest and agricultural and processing techniques, and so on [84].

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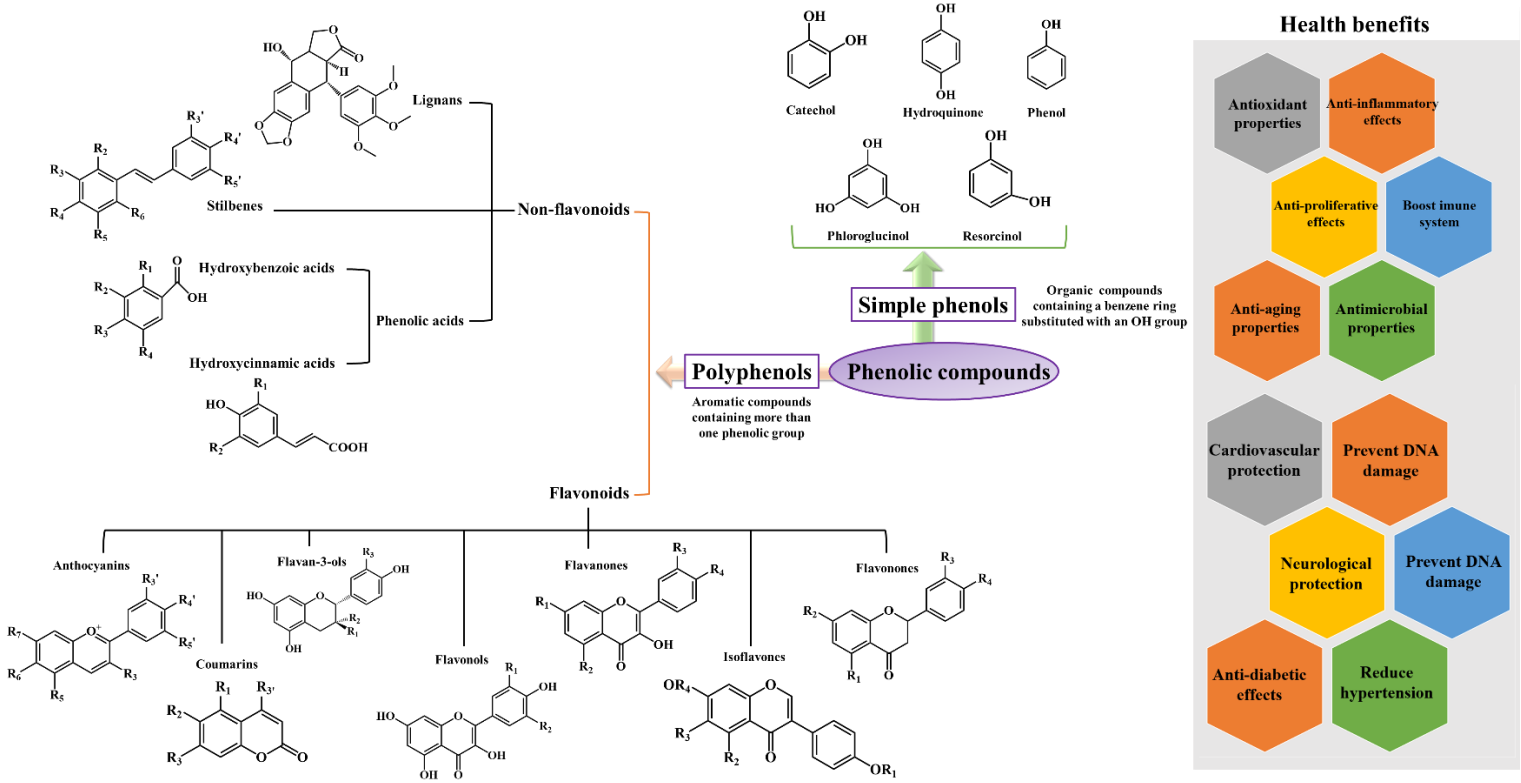

Figure 1. Main dietary polyphenols and simple phenols, and also their most notable health-benefits (OH: hydroxyl group) (adapted from Mamari [30], Gonçalves et al. [31] and Matsumura et al. [32].

Table 1. Main polyphenols found in nature and their phenolic-rich sources.

Polyphenols	Sources	References
Non-flavonoids		
Lignans	Flaxseeds	[85]
Phenolic acids		[86–89]
Hydroxybenzoic acids	Black radish, onions, and tea	
Hydroxycinnamic acids	Cereals, coffee, fruits, tea, vegetables and wine	
Stilbenes	Grapevines, peanuts and sorghums	[90]
Flavonoids		

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Anthocyanins		[46,51,58,64,91–102]
Cyanidin	Sweet and sour cherries, mulberries, black elderberries, chokeberries and red cabbage	
Delphinidin	Eggplant, roselle, maqui berries and black currants	
Pelargonidin	Raspberries and strawberries	
Peonidin	Cranberries, blueberries and plums	
Petunidin	Chokeberries	
Malvidin	Acerola, blackberries and grapevines	
Coumarins		[70,103,104]
Umbelliferone	Aegle marmelo	
Esculin	Horse-chestnut barks	
Flavan-3-ols		[71,86,105–107]
(+)-Catechin	Peaches, apricots, apples and green tea	
(-)-Epicatechin	Apricots, sour cherries, apples, cholate, cocoa and green and black teas	
Epigallocatechin gallate	Green tea	
Flavonols		[75,77,78,108–111]
Kaempferol	Onion leaves, papaya shoots, pumpkins, carrots and black tea	
Quercetin	*Mentha pulegium* L.	
Myricetin	Whortleberries, lingonberries, chokeberries and cranberries	
Fisetin	Strawberries, apples, persimmons, grapes, onions, and cucumbers	
Flavanones		[112–116]
Hesperetin	Citrus fruits, namely, grapefruits, tangerines, oranges and lemons	
Naringin	Citrus fruits, namely grapefruits and oranges	
Eriodictyol	Yerba Santa	
Flavonones		[117–120]
Hesperidin	Citrus fruits	
Liquiritin	*Glycyrrhiza Glabra* L. leaves and roots	
Pinocembrin	Honey and propolis	
Isoflavones	Soybeans	[68,121–125]

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4. Pharmacological Properties of Dietary Polyphenols

Knowing the deleterious effects caused by oxidative stress and exacerbated inflammatory responses, it is not surprising that these natural molecules, which are composed of many hydroxyl groups, can easily neutralize radical species or breaking chains, by giving an electron or hydrogen atom, and interfere with inflammatory pathways, and thus, contributing to increase immunity defences and promote a healthy status. In addition, evidence also refers that they are effective in acting as anti-aging, anti-microbial and antiproliferative agents, and possess abilities to increase insulin sensitivity, lower blood sugar levels and ameliorate brain and heart functions, and digestion, too.

As expectable, their benefits are closely linked to their chemical structure and also quantities. Indeed, several studies already reported that, in most cases, an increment in phenolics enhances the biological potential [40,46,48,126–131]. Therefore, it is not surprising that their interest is increasing worldwide, specially to prevent and/or attenuate several diseases, especially those without medical cure, like AR (Figure 2). In this disease, there is verified a network of inflammatory components, degrading enzymes, angiogenic molecules and cells. Altogether, this originates immune deregulation, which, without surprise, is not only associated with exacerbated inflammatory responses but also with oxidative stress, affecting particularly with nuclear factor erythroid 2–related factor 2 (Nrf2) pathway (discussed below). Phenolics have been showed potential to counteract oxidative stress levels, and down-regulate exacerbated inflammatory responses, and thus, their use as adjuvant therapy and/or combined with chemical pharmaceutics can be very useful. Similar approaches have been applied in cancer treatment. In fact, in 2019, from the 247 anticancer drugs available, 200 were from natural products, while 38 were synthetic drugs and 9 were vaccines [29].

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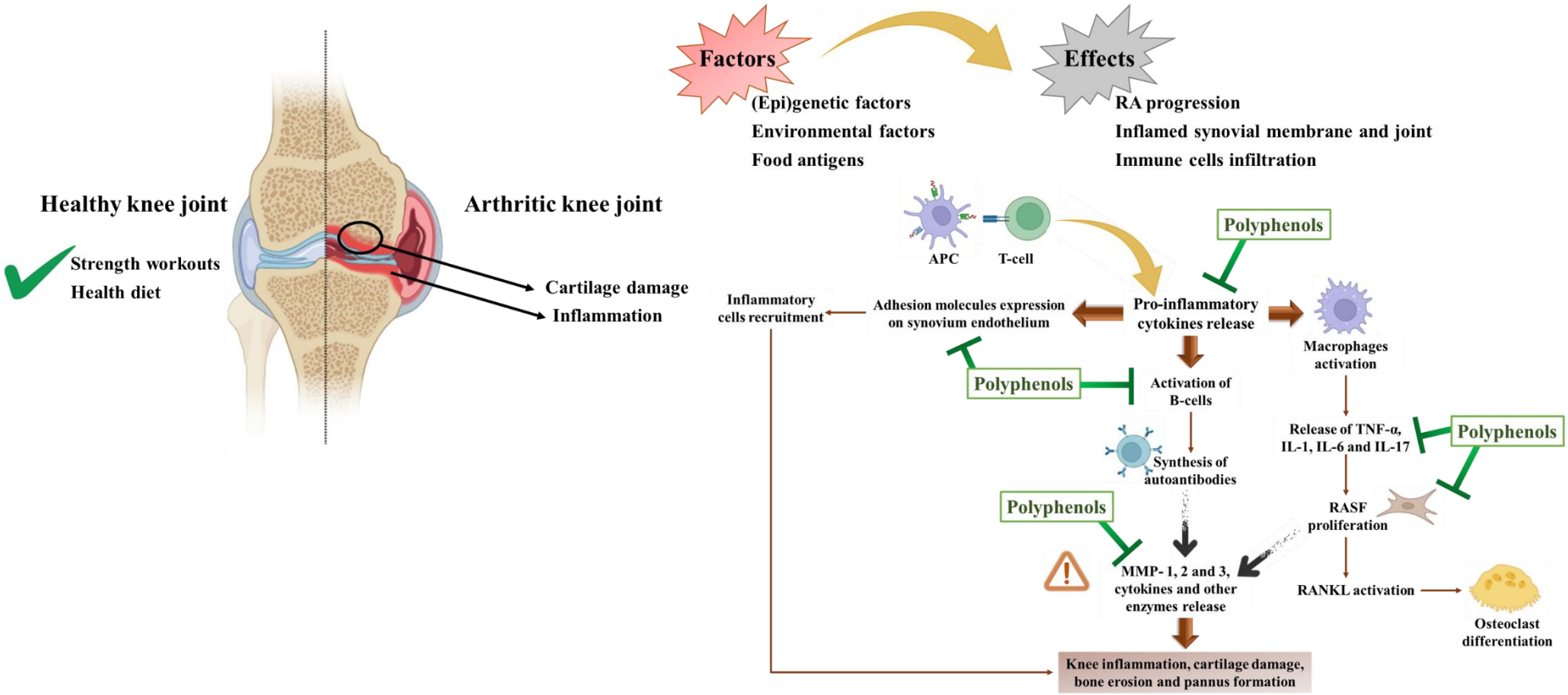

Figure 2. Effects of polyphenols against rheumatoid arthritis (RA: rheumatoid arthritis; APC: antigen-presenting cell; IL: interleukin; TNF-α: tumor necrosis factor alpha; MMP: matrix metalloproteinases; RASF: rheumatoid arthritis synovial fibroblasts; RANKL; receptor activator of nuclear factor kappa-B ligand) [Portions of Figure 2 were drawn using images from BioRender.com (https://biorender.com/) (accessed on 8 March 2024)] (adapted from Weyand & Goronzy [132] and Long et al. [6]).

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4.1. Antioxidant Capacity

Reactive oxygen and nitrogen species, namely superoxide and nitric oxide radicals, play a vital part in human body, being signaling molecules and interfering in immune responses and signal transduction pathways, cells growth and gene expression. However, their overproduction and accumulation, have a negative impact on mitochondria and lead to the formation of more toxic free radical species, such as peroxynitrite and peroxyl radicals, promoting deleterious effects in cells, DNA mutations, disintegration and protein damage of membranes, and alterations in phagocyte-mediated activity, playing a pathogenic role in chronic inflammatory diseases. Consequently, inflammation signalling cascades and oxidative stress components are triggered, which in turn, enhance the risk of neuropathologies and chronic diseases, as atherosclerosis, cancer, metabolic syndrome, and of course, RA [133,134].

Regarding RA, its pathophysiology has been linked to oxidative stress, principally with the Nrf-2 pathway. This one is the major pathway involved in the maintenance of homeostatic responses by rising intracellular defence mechanisms and regulating the heme oxygenase-1 axis, control macrophages activation and NF-κB pathway, reducing stress oxidative and inflammation [135]. Under quiescent conditions, Kelch-like ECH-associated protein 1 (Keap 1) holds Nrf2 in the cytoplasm, promoting its ubiquitination and subsequent proteolysis; however, under pathology conditions, Nrf2 is released from Keap1, and goes inside to the nucleus, where happens the transcription of antioxidant enzymes [136–138].

Among the most promising therapeutic and adjuvant approaches, polyphenolics assume a prominent interest, since they already showed notable capabilities to restore oxidative stress and inflammation near basal levels, by interact with Keap1 protein, avoiding its linkae with its binding site in Nrf-2 and subsequently, cause the dissociation of Keap1 from Nrf2, leading to the transcriptional activation of Nrf-2, and hence, stimulating intracellular antioxidant enzymes (glutathione, catalase and superoxide dismutase) activity, and, of course, neutralizing oxidative stress [136–138].

In a general way, and in order to establish the antioxidant properties of phenolics, three statements were recently proposed, known as Bors criteria (Figure 3). The first one is the most significant, and it refers that, due to hydrogen bonding the presence of a catechol group on B ring, increases the stability of phenolics, and consequently, their antioxidant properties. The second one is the existence of a 2,3 double bond combined with a 4-oxo group on C ring, which in turn, facilitates electron delocalization and allows a better aryloxyl radical stabilization, while the third one is related to the presence of OH groups at positions 3 and 5 on A and C rings combined with a 4-oxo group on C ring, allowing electron delocalization via hydrogen bonds [139]. Thus, these characteristics make phenolics capable of acting as electron and hydrogen donors [140,141]. Among phenolics, quercetin and myricetin complete all Bors criteria, and hence, they are well-known due to their notable capacity to reduce radicals [142]. Moreover, the existence of the catechol group in quercetin and its derivatives enhances their biological potential [139].

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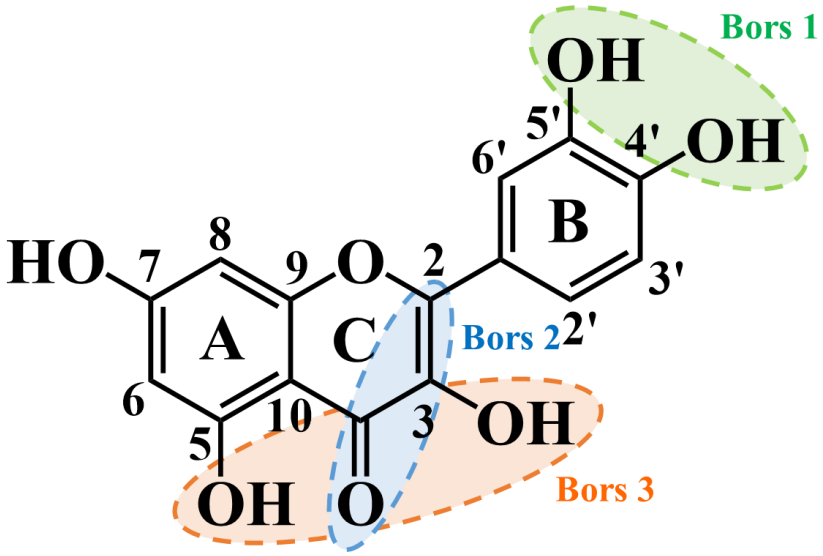

Figure 3. Representation of phenolics antioxidant abilities explained by Bors criteria, involving their structure. Bors 1: catechol group on the B ring (green); Bors 2: 4-oxo group and 2,3 double bond on the C ring (blue); Bors 3: hydroxyl (OH) groups at 3 and 5 groups on A and C rings combined with a 4-oxo group on C ring (adapted from Platzer and co-workers [139] and created with ChemDraw Professional 16.0 (CambridgeSoft, Perkin Elmer Inc., Waltham, MA, USA).

Regarding non-flavonoid compounds, hydroxycinnamics showed better antioxidant capacities than hydroxybenzoic acids due to the CH=CH-COOH group, the 7,8-double bond, the carboxyl group with O-alkyl esters and the presence of hydroxyl groups at the ortho and/or para-positions [141,143–145]. For lignans, it is well-established their capacity to eliminate radicals and free species is mainly due to the presence of catechol groups [146], while the hydroxylation at position 4 and hydroxyl groups at the ortho position are the main contributors for the antioxidant potential attributed to stilbenes [147].

Comparing with flavonoids, these last ones are more effective in eliminating free species and radicals than non-flavonoids, not only due to the presence of more hydroxyl groups, but also owing to the double bond in positions 2 and 3, the o-diphenolic group and 3’,4’-catechol hydroxyl groups on B ring and the conjugation between the double-bond and the 4-oxo group on C ring [145,148].

Even so, it is important not to forget that catechol and pyrogallol groups also make phenolics vulnerable to autoxidation, particularly when they interact with transition metals; however, the glycosylation and methylation of hydroxyl groups can decline this harmful behaviour [149–152]. Furthermore, pH also influences the antioxidant properties of phenolics; in fact, and although lower pH levels increase iron-reducing activity, they diminish iron catalytic activity and chelate activities [153].

Focusing on their potential to interact with Nrf-2 pathway, Diniyah and colleagues [154] revealed that catechin, epicatechin and gallic acid from non-oilseed legumes present high binding affinities with Keap1, a protein that activates the degradation of Nrf-2, being, therefore, promising new Nrf2 activators. Similar results were found involving hesperetin, hesperidin, naringenin, naringin, narirutin, neohesperidin, neohesperidin dihydrochalcone and nobiletin citrus-derived flavonoids [155], and sesamol isolated from Sesamum indicum L. seed oil [137]. Mice treated with 37.5, 75, and 150 mg/kg green tea every 8 h by intragastric administration that, were then, sacrificed after 4,12 and 20 h after administration, showed higher levels of antioxidative enzymes and liver phase II enzymes; in addition, docking studies revealed that the most predominant compounds on this tea, which were, caffeine, catechin, catechin gallate, epicatechin, epigallocatechin, epigallocatechin gallate, epicatechin gallate, gallic acid and gallocatechin revealed strong binding affinities with the Keap1 protein [138]. In accordance with the mentioned, the daily intake of 25 mg/kg/body weight (bw) epigallocatechin gallate by rats with lung injury and oxidative stress induced by fluoride displayed capability to increase antioxidant status and Nrf2 gene expression,

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and reduce inflammatory cytokine [156]. Similar results were obtained using endothelial cells pre-treated with polychlorinated biphenyls 126 [157]. Furthermore, Li et al. [136] verified that concentrations of apigenin, cyanidin 3-sambubioside, echinacoside, luteolin 5-O-glucoside, quercetin 3-O-rutinoside and α−tocopherol at 10 and 50 μM can effectively enhance Nrf-2 levels in the nucleus of hydrogen peroxide−induced oxidative-injured rat adrenal pheochromocytoma PC12 cells. 10-100 μM 5-caffeoylquinic acid also demonstrated to be a potent Nrf-2 activator in human hepatocellular carcinoma HepG2 cells [158]. Finally, Mishra and colleagues revealed that the combination of curcumin (30 mg/kg/bw) with vitamin E (200 mg/kg/bw) could be very effective in counteract oxidative stress in hypothyroid rats with via interfering with NF-kB/AKT/mTOR/KEAP1 [159].

Moreover, positive correlations were already reported between polyphenol amounts and the biological potential. Particularly, positive correlations were already reported between sweet cherry anthocyanin-rich fractions against nitric oxide, superoxide radicals (r> 0.9013) [43], ferric species (r=0.739), and between TPC, and non-colored and colored fractions from sweet cherry fruits and hydrogen peroxide (r> 0.940) [48]. Additionally, a high correlation (r=0.7581) between honey TPC and the elimination of nitric oxide radicals was also found [134,160], and between total flavonoids amounts of sweet cherries vegetal parts and the inhibition of hemoglobin oxidation (r> 0.9636) [161].

Focusing on individual compounds from honey, high correlations were found between caffeoyl hexose, quercetin 7-glucoside-3-O-rutinoside, quercetin derivative and quercetin acetyl rhamnoside and •NO scavenging potential (r> 0.7581) and concerning quercetin 3-O-rutinoside and hemoglobin oxidation, hemolysis and lipid peroxidation (r > 0.7355). Additionally, positive correlations were also reported between caffeoyl hexose and quercetin acetyl rhamnoside and lipid peroxidation (r=0.7352 and r=0.755, respectively) [160], whereas a mild correlation (r=0.64) between quercetin content of pollen extracts and protective effects against oxidative injury induced by AAPH on Hepa1-6 hepatic cells was also reported [162]. On the other hand, strong correlations were found involving quercetin 3-O-glucoside (r=0.8640), and ϱ-coumaric acid derivative 1 (r=0.9444), ϱ-coumaroylquinic (r=0.8646), ϱ-coumaric (r=0.8012) and 5-O-caffeoylquinic (r=0.9907) acids of sweet cherries and nitric oxide scavenging test, and also involving this last hydroxycinnamic and superoxide radicals (r=0.9958) [134,163](, as well as between malvidin, delphinidin 3-O-arabinoside and 5-O-caffeoylquinic acid and the antioxidant potential showed by blueberry fruits (r> 0.8689) [163].

Considering all the mentioned data, phenolics seem to help prevent and/or attenuate RA by improving oxidative stress-related chronic diseases, chiefly owing to their interaction with Keap1-Nrf2 complex, activating Nrf-2 transcription. Even so, it is important to highlight that, in many cancer types, the activation of Nrf-2 is predominantly associated with drug resistance, which in turn, *diminishes* chemotherapy effects and promotes metastatic invasion of cancer cells [164–166]. Given that, several attempts have been conducted in order to reduce Nrf-2 levels [167,168]. Considering it, chrysin, luteolin, resveratrol, clofarabine, and 3′,4′,5′,5,7-pentamethoxyflavone already showed to possess promising inhibitory activities, revealing half maximal inhibitory concentrations (IC_{50}) of 10.20, 1.5-40, 15, 15, and 10-400 μM, as well as ability to reduce heme-oxygenase 1 [169–172]. Moreover, agrimoniin isolated from Agrimonia pilosa Aitch (IC_{50} values of 100, 200, 300 μM), galloyl glucoses-1,2,3,4,6-penta-O-galloyl-β-D-glucose and 1,3,6-tri-O-galloyl-β-d-glucose isolated from Excoecaria formosana, schisantherin A isolated from Fructus schisandrae (IC_{50} = 2.5 μM), neferine isolated from leaves of Nelumbo nucifera Gaertn. (IC_{50}=0-20 μM) and wedelolactone isolated from Eclipta prostrate Lour (IC_{50}=2.5–20 μM) are also effective in reducing cancer cells' proliferation [102,166,168,173,174]. Finally, Castanea crenata Siebold & Zucc, Cinnamomi Cortex, together with procyanidins isolated from it, and rosemary extracts, Chrysanthemum zawadskii and Licorice Glycyrrhiza uralensis, Bergenia ligulata and Rhododendron luteum sweet extracts, and strawberry tree honey also showed similar effects [164,165,167,175–180], as well as pterostilbene, a natural dimethoxylated analog of resveratrol [181].

4.2. Anti-Inflammatory Abilities

During inflammation, IL-1 and IL-6, tumor necrosis factor (TNF-α), prostaglandins, heat shock proteins, and nitric oxide and superoxide radicals are generated, which, in part, help in controlling

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this process by activating neutrophils and macrophages [43]. Hydrogen peroxide is also released, owing to the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) kinases and oxidation, and hence, stopping reactive species accumulation [182,183]. However, and although inflammatory processes are directly linked to individuals' development, when these responses are exaggerated, carbohydrates damage, lipid peroxidation protein and nucleic acids oxidation happen, contributing to the onset of many disorders, including AR [184–186]. Once again, and given phenolics can counteract oxidative stress and normalize immune responses, it is not surprising that phenolics are a target of extensive research. In fact, they already showed capabilities to diminish the activity of COXs, lipoxygenase and iNOS, by interfering with different stages of the *inflammatory* cascade, namely by down-regulating NF-kB and activating protein-1, and *stimulating* Nrf-2, mitogen-activated protein kinase (MAPK), a protein complex *responsible* to modulate a group of protein kinases that play an essential role in signal transduction by modulating gene transcription in the nucleus, and protein kinase-C [187–190]. In fact, the inhibition of NF-kB is crucial to attenuate inflammatory responses once this complex of proteins is the main responsible *for controlling* the expression of many genes involved in inflammation, including IL-1, IL-2, IL-6, and TNF-α, COX-2, vascular endothelial growth factor (VEGF), IL-8, MIP-1α, and MCP-1 chemokines, immuno-receptors and adhesion molecules. In this way, phenolics can reduce reduce the severity of inflammation [191–193].

Within polyphenols, apigenin, catechin, ellagic acid, epigallocatechin gallate, epigallocatechin gallate, homoplantaginin, luteoloside, quercetin aglycone, quercetin 3-O-rutinoside, allopurinol, resveratrol and tangeretin already showed notable anti-inflammatory effects [157,194–199]. Moreover, curcumin, kaempferol 3-O-sophoroside, epigallocatechin-gallate, lycopene and oleanolic acid are effective in inhibiting high mobility group box 1 protein, which is an important chromatin protein involved in the transcription of nucleosomes, transcription factors and histones related to inflammatory processes [200–203]. Resveratrol can downregulate inflammatory pathway activated by TNF-α in articular chondrocytes [204].

On the other hand, caffeic acid (10 μg/mL), hydroxybenzoic derivatives (25 μg/mL), ϱ-coumaric acid (50 μg/mL) and quercetin (100 μg/mL), already showed capabilities to suppress MAPK, JNK1 phosphorylation and NF-κB, and hence, down-regulate the activity of COX-2 and inducible nitric oxide synthase, and consequently, diminish the production of prostaglandins and nitric oxide radicals, respectively [205,206]. In addition, caffeic acid phenethyl ester can also avoid the activation of toll-like receptor (TLR)-4 activation and lipossacharide-mediated NF-κB in macrophages [207].

Catechin and epicatechin (1.7-17.2 μM) can also modulate phorbol 12-myristate 13-acetate-induced NF-kB activation in Jurkat T cells [208]. Particularly, quercetin can inhibit the biosynthesis of leukotrienes in human polymorphonuclear leukocytes, and the activation of NF-kB and p38 MAPK in human mast cells, by preventing the degradation of Iκ Bα and the nuclear translocation of p65, and hence it can reduce IL-1β, IL-6, IL-8 and TNF-α expression [209], as well avoid iNOS gene expression by blocking the activation of IkK kinases, NF-kB and STAT1 in mouse BV-2 microglia [210]. This one can also modulate chromatin remodeling, by blocking the recruitment of CBP/p300 to the promoters of interferon-inducible protein 10 macrophage inflammatory protein-2 genes in primary murine small intestinal epithelial cells [211]. On the other hand, kaempferol and galangin display identic properties concerning epicatechin effects in mouse BV-2 microglia [212,213].

As well as epicatechin, epigallocatechin gallate can also avoid IkK kinases activation, avoiding the degradation of Ik-Bα in culture respiratory epithelial cells and in rat models [214], and blocking DNA binding of NF-κB, and hence, diminishing IL-12 p40 and iNOS expression in murine peritoneal macrophages and J774.1 macrophage cells [187,215]. Furthermore, 10, 25, 50 and 100 μM epigallocatechin gallate also showed capacity to attenuate COX-2 expression, without affecting COX-1, in colon cancer PC-3 cells [216], as well as ability to block NF-κB activation in human epithelial cells and reduces iNOS expression, and consequently, nitric oxide radical levels in macrophages at doses of 5 and 10 μM [217]. Furthermore, and likewise genistein [218], luteolin can also suppress the activation of NF-kB and the expression of proinflammatory genes and IKK kinases in murine

 doi:10.20944/preprints202404.0585.v1

macrophages RAW 264.7 and mouse alveolar macrophages, as well as TNF-α secretion in co-cultured intestinal epithelial Caco-2 and RAW 264.7 cells [219,220].

On the other hand, 25, 50, and 100 μM chebulanim, a natural polyphenol acid isolated from Terminalia chebula Retz could inhibit the nuclear translocation of p38 and p65 in liposaccharide-stimulated macrophages, in a dose-dependent manner [185]. Additionally, aqueous birch leaf extract of Betula pendula inhibits the growth and cell division of inflammatory lymphocytes in a dose-dependent manner due to apoptosis induction [221].

Furthermore, hydroxytyrosol and resveratrol, two polyphenols largely abundant in olive oil and red wine can also downregulate NF-kB and the expression of vascular cell adhesion molecule-1 in umbilical veins stimulated with liposaccharide at doses varying between 1 and 100 μM/L [222]. Moreover, anthocyanins, namely cyanidin derivatives (125 μg/mL) demonstrated more efficacy in reducing COX-2 levels than naproxen (10 μM) and ibuprofen (10 μM) (47.4%, 41.3% and 39.8%, respectively) [223]. In silico tools also revealed high energy bindings of cyanidin 3-O-rutinoside (−11.4 kcal/mol), kaempferol 3-O-rutinoside (−10.8 kcal / mol) and cyanidin 3-O-glucoside (−10.1 kcal/mol) with iNOS [148]. Furthermore, homoplantaginin, luteoloside, quercetin, quercetin 3-O-rutinoside, allopurinol and resveratrol already showed potential, both in vitro and in vivo, ability to suppress NLRP3 and/or TLR4 inflammasome activation [194,196–199].

Relatively to in vivo studies, the daily gestion of cherries (141 g) for 10 days by rats and ringdoves down-regulate IL-1β and TNF-α pro-inflammatory cytokine levels, and raise IL-4 and IL-2 anti-inflammatory cytokines [224]. In addition, gingerenone A (10 mg/kg/bw), a polyphenol largely present in ginger, also displayed positive effects in suppresses obesity and adipose tissue inflammation by avoiding macrophage infiltration and enhance adiponectin, high-fat diet-fed mice which were treated during 15 weeks [225], as well as quercetin [226]. On the other hand, apigenin can stop inflammation in human THP-1-induced macrophages and mouse J 774A, by reducing IL-1β production, via inhibiting the activation of caspase-1 through the disruption of NLRP3 inflammasome, as well as diminishing TNF-α and IL-1β thanks to its ability to inactivate NF-kB [195]. Apigenin, as well as other polyphenol compounds extracted from chamomile, meadowsweet and willow bark, including quercetin and salicylic acid (0-100 μM)also revealed ability to decrease IL-1β, IL-6 and TNF-α in THP-1 macrophages and also protect them against oxidative damage [227]. Tannic acid-based nanogel is also an efficient anti-inflammatory agent, showing a notable potential to reduce neutrophil recruitment and pro-inflammatory cytokines, indicating successful alleviation of inflammation [228].

Moreover, curcumin can easily interfere with NF-κB, as well as with STAT3, reducing the expression of TLR-2 and -4, and upregulating peroxisome proliferator-activated receptor ɣ, as observed in male rats that were treated with 0.2 μM curcumin for 3 days [229,230].

Among fruits, sweet cherry phenolic-rich fractions can reduce nitric oxide radicals and decrease iNOS and COX-2 expression in RAW macrophages stimulated with lipopolysaccharide [28]. Moreover, aqueous and hydroethanolic extracts of their vegetal parts also are effective in inhibiting nitrite levels in a dose-dependent manner in these cell lines [26]. Moreover, some Brazilian plants also showed potential to reduce TNF-α and CCL2 levels in lipopolysaccharide-stimulated human monocytic THP-1 cells [231]. Regarding individual compounds, ferulic and coumaric acids, which are largely found in Chinese propolis, Lonicera japonica Thunb) and Kalanchoe gracilis showed similar capacities [232–234]. In addition, 1-1000 μg/mL quince (Cydonia oblonga Miller) peel polyphenols modulate liposaccharide-induced inflammation in human THP-1-derived macrophages, reducing IL-6 and increasing IL-10 expression via inhibiting NF-κB, p38MAPK and Akt pathways [235].

Focusing on clinical trials, has already been reported that the daily consumption of cherries (280 g) by women can reduce plasma C-reactive protein and nitric oxide radicals, 3 h after intake [236].

4.2.1. Anti-Rheumatoid Effects

As expectable, polyphenols and polyphenolic-rich sources also reveal promising abilities to attenuate, or even prevent, rheumatoid arthritis, as described in Table 2.

 doi:10.20944/preprints202404.0585.v1

In Vitro Studies

Considering all the mentioned until now, it is not surprising that polyphenols can be considered promising molecules in preventing and/or attenuating rheumatoid arthritis.

So far, and focusing on in vitro assays, it has been already reported that slibinin, a natural flavonoid extracted from milk thistle (Silybum marianum) showed effectiveness in inhibiting Th17 cell differentiation and induce macrophage M2 polarization in RAW 264.7 cells, and promotes apoptotic events and inhibits NF-kB, SIRT1 and autophagy in fibroblast-like synoviocytes at doses of 50, 100 and 200 μM [237]. Moreover, 50, 100 and 200 μg/mL oleuropein, the most common polyphenolic detected in olive leaves showed potential to shift $CD4^+$ T cells from peripheral blood mononuclear cells of RA patients toward $CD4^+CD25^+$FoxP3 Tregs and induce the production of IL-10 and TGF-β [238]. In addition, 12.5-50 μg/mL polyphenolic extract from extra virgin olive oil inhibits the inflammatory response in IL-1β-activated synovial fibroblasts, as well as TNF-α, IL-6, COX-2 and microsomal PGE synthase-1 production, thanks to their capability to downregulate MAPK and NF-kB signalling pathways [239].

Moreover, 5 and 10 μM curcumin showed effectiveness in reducing survivability, and decreasing levels of MMP1 and TNF-α in synovial sarcoma SW982 cells, considered the best in vitro approach to study RA [240]. Additionally, 25-100 μM curcumin can induce apoptosis and inhibit PGE2, by down-regulating anti-apoptotic Bcl-2 and the X-linked inhibitor of the apoptosis protein and upregulating pro-apoptotic Bax expression, in a concentration-dependent manner, on synovial fibroblasts obtained from patients with RA [241]. In addition, this compound at 12.5-50 μM, also showed capacity to reduce IL-1β, PMA-induced IL-6 and VEGF-A expression, by inhibiting NF-κB and induced dephosphorylation of ERK1/2 and enhancing apoptosis in both in MH7A cells and RA-fibroblast-like synoviocytes [242].

On the other hand, 1, 5 and 25 μM quercetin diminish IL-17-stimulated RANKL production in RA-fibroblasts-like synoviocytes, IL-17-stimulated osteoclast formation and Th17 differentiation, and hence, modulate bone destructive processes in RA [243]. 12.5-100 μM Punicalagin, a natural polyphenol extracted from pomegranate juice, also showed capability to reduce IL-1β, IL-6, IL-8, IL-17A, MMP-1 and MMP-13 in fibroblast-like synoviocytes [244].

Additionally, 25, 50, 100, 250, and 500 μM syringaldehyde, a small polyphenolic compound extracted from Capparis spinosa L. showed potential to diminish CD86, CD40, MHC II and IL-23 expression, and enhance IL-10 expression and antigen phagocytosis on human acute lymphoblastic leukemia T lymphocytes, via inhibiting MAPK/NF-kB signalling pathways [245].

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Table 2. Main effects attributed to polyphenolic exposition and daily treatment.

Polyphenolic/ Plant	Model	Dose	Effects	References
In vitro studies				
Slibinin	RAW 264.7 cells	50, 100 and 200 μM	Th17 cell differentiation inhibition NF-*k*B, SIRT1 and autophagy inhibition Macrophage M2 polarization induction Apoptotic events promotion	[237]
Oleuropein	Peripheral blood mononuclear cells of RA patient cells	50, 100 and 200 μg/mL	↑ IL-10 and TGF-β Shift $CD4^+$ T cells from peripheral blood mononuclear cells of RA patients toward $CD4^+CD25^+$FoxP3 Tregs	[238]
Extra virgin olive oil	Synovial fibroblasts	12.5-50 μg/mL	↓ IL-1β, TNF-α, IL-6, COX-2 and microsomal PGE synthase-1, and MAPK and NF-*k*B signalling pathways	[239]
Curcumin	Synovial sarcoma SW982 cells	5 and 10 μM	↓ MMP1 and TNF-α	[240]
Quercetin	RA-fibroblasts-like synoviocytes	1, 5 and 25 μM	↓ IL-17-stimulated RANKL production IL-17-stimulated Osteoclast formation Th17 differentiation Modulate bone destructive processes in RA	[243]
Punicalagin	Fibroblast-like synoviocytes	12.5-100 μM	↓ IL-1β, IL-6, IL-8, IL-17A, MMP-1 and MMP-13	[244]
Syringaldehyde	Lymphoblastic leukemia T lymphocytes	25, 50, 100, 250, and 500 μM	↓ CD86, CD40, MHC II and IL-23 ↑ IL-10 and antigen phagocytosis Inhibition MAPK/NF-*k*B signaling pathways	[245]
Resveratrol	Fibroblast-like synoviocytes	1, 3 and 10 μg/mL	↓ Sirt1 protein, MMP1 and MMP13	[246]

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Resveratrol	Fibroblast-like synoviocytes	20 μM	Inhibition of phosphorylation and acetylation of p65, c-Jun, and Fos ↓ COX-2 expression	[247]
Resveratrol	Fibroblast-like synoviocytes	1-40 μM	↑ Nrf2-2, heme oxygenase-1, and Bcl-2/Bax, apoptosis ↓ Keap1 expression and ROS, and MDA levels block NF-κB p6 translocation, Inhibit cell proliferation and migration	[248,249]
Resveratrol	RSC-364 cells	25 and 50 μmol/L	↓ Hypoxia-inducible factor-1α and activated phosphorylation of p38 MAPK and c-Jun N-terminal kinase arrest cells at G0/G1 cell-cycle ↑ apoptosis	[250]
Resveratrol	U251 glioma cells	1-100 μM	Interference on PI3K/Akt/BAD signalling pathway Inhibition of cells growth and apoptosis	[251,252]
Resveratrol	Human umbilical vein endothelial cells	20 μM	interference on PI3K/AKT and MEK/ERK Induce FOXO transcriptional activity Inhibition of cell migration and capillary tube formation Prevent angiogenesis	[253]
Resveratrol	Fibroblast-like synoviocytes	50 μM	Block cells at the G2/M stage ↓ TNF-α and S phase cells ratio Promote serine-threonine kinase-p53 axis, and autophagy Cells apoptosis	[254]
Resveratrol	Human RA synovial MH7A cells	100 and 200 μM	↓ cells viability Stimulate H2A.X phosphorylation and apoptosis events Mitochondrial membrane potentials disruption Stimulate cytochrome c release from the mitochondria to the cytosol Caspase-3 and caspase-9 activation	[255]

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			Upregulate the expression of the NAD-dependent deacetylase SIRT1 mRNA Downregulate the expression of the Bcl-X(L) mRNA Hyperplasia suppression	
Resveratrol	Fibroblast-like synoviocytes	200 μM/L	Caspase-3 activation Inhibition of cells proliferation Induces cell apoptosis	[256]
Resveratrol	Fibroblast-like synoviocytes	25-200 μM	↓ ROS and Bax ↑ Bcl-2 levels and apoptotic cells Regulate the expression of mitochondrial superoxide dismutase	[257]
Resveratrol	Fibroblast-like synoviocytes	100 μM	↓ MMP-1, MMP-3, MMP-9, RANKL, osteoprotegrin	[258]
Resveratrol	Fibroblast-like synoviocytes	100 μM	↓ TNF-α by interfering with SIRT1/cortistatin pathway	[259]
Resveratrol	Fibroblast-like synoviocytes	100 μM	↑ the expression *of* genes involved in mitosis, cell cycle, chromosome segregation and apoptosis	[260]
Resveratrol	Fibroblast-like synoviocytes	5, 15 and 45 mg/kg	↓ IL-1, IL-6, IL-8 and TNF-α ↑ IL-10 and apoptosis	[261]
Resveratrol	Fibroblast-like synoviocytes	10 and 20 μM	↓ urban particulate matter-induced COX-2/PGE2 release Inhibition of the activation of NADPH oxidase/ROS/NF-κB	[262]
Resveratrol	Mouse preosteoblastic MC3T3-E1 cells	1, 2, 3 and 5 μM	Mediate SIRT-1 interactions with p300 Modulate NF-*k*B signaling activation Inhibition of osteoclastogenesis Prevent bone loss in bone-derived cells	[263]

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Resveratrol + methotrexate	Synovial mononuclear cells from RA patients	25 μM resveratrol with 0.5 μg/mL methotrexate	↓ monocyte chemoattractant protein 1 levels	[264]
Curcumin	Fibroblast-like synoviocytes	25-100 μM	Induce apoptosis PGE2 inhibition Downregulate anti-apoptotic Bcl-2 and the X-linked inhibitor of the apoptosis protein Upregulate pro-apoptotic Bax expression	[241]
Curcumin	Fibroblast-like synoviocytes and MH7A cells	12.5-50 μM	↓ IL-1β, PMA-induced IL-6 and VEGF-A expression, and cells viability Inhibition of NF-κB and induced dephosphorylation of ERK1/2 ↑ apoptosis	[242]
Purified grape-derived compounds	1, 10 and 100 μM	Human peripheral blood mononuclear cells	↓ TNF-α, IL1, IL-6 and iNOS genes	[100]
Gallotannins	Human mast cells	1, 1 and 10 μg/mL	Downregulate NF-*k*B expression	[265]
Ellagic acid	Fibroblast-like synoviocytes	10, 25, 50 and 100 μM	↓ IL-6, IL-1β, MDA and TNF-α ↑ Superoxide dismutase and apoptosis	[266]
Gallic acid	Fibroblast-like synoviocytes	0.1 and 1 μM	↑ caspase-3 activity Regulate Bcl-2, Bax, p53 and pAkt productions ↓ IL-1β, IL-6, CCL-2/MCP-1, CCL-7/MCP-3, COX-2, and MMP-9	[267]
Rosmarinic acid nanoparticles	Macrophages	Not mentioned	↓ RONS and pro-inflammatory cytokines	[191]
ρ-Coumaric acid encapsulated with	Macrophages	Not mentioned	↓ RONS and pro-inflammatory cytokines Inhibition of osteoclasts differentiation	[268]

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mannosylated liposomes			Downregulate the expression of MMP-9 and NFATc1	
Ferulic acid	Fibroblast-like synoviocytes	25-300 μM	↓ IL-17-levels Inhibition of IL-17/IL-17RA/STAT-3 signalling cascade	[269]
Ferulic acid	RAW 264.7 macrophages	25, 50 and 100 μM	Attenuate RANKL-induced osteoclast differentiation ↓ bone resorption activity Downregulate NFATc1, c-Fos, TRAP, Cathepsin K and MMP-9 levels	[270]
Chlorogenic acid	T cells c1	10-50 μg/mL	Inhibition of osteoclast differentiation and bone resorption Downregulate RANKL Suppress mRNA expression of NFATc1, TRAP and OSCAR	[271]
Tea polyphenol carrier-enhanced dexamethasone	Umbilical vein endothelial, murine fibroblast cells L929 and murine macrophage RAW 264.7 cells	Not mentioned	↓ inflammatory	[272]
Tinospora cordifolia	RAW 264.7 cells	100, 250 and 500 μg/mL	↓ IL-6, TNF-α, PGE2, and NO, and iNOS and COX Modulate JAK/STAT pathway	[273]
Blueberry polyphenols	HIG-82 rabbit synoviocytes	100-200 μM	↓ TNF-α, IL-1β, MMP3 and NF-*k*B levels	[274]
Cocoa polyphenols	Mouse epidermal cells	10 and 20 μg/mL	↓ TNF-α-induced vascular endothelial growth factor expression Inhibition PI3K and MEK1	[275]
Catechin-7,4'-O-digallate from *Woodfordia uniflora*	Mouse macrophages	5-80 μM	↓ IL-6 and IL-1β levels Regulate NF-*k*B signalling pathway	[276]

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Salacia reticulata leaves	MTS-C H7 cells	IC_{50} score of ~850 μg/mL	Inhibition of cells proliferation	[277]
In vivo studies				
Slibinin	Rats with induced RA	50, 100 and 150 mg/kg	↓ IL-1β, IL-6 and TNF-α levels, and joint inflammation	[237]
Resveratrol	Rats with induced RA	5 mg/kg, 15 mg/kg and 45 mg/kg	↓ abnormal proliferation of fibroblast-like synoviocytes, swelling degree of the paw and malondialdehyde levels ↑ superoxide dismutase activity, and glutathione peroxidase and glutathione reductase ratio	[278]
Resveratrol	Rats with induced RA	10 mg/kg	↓ progression of periodontitis and rheumatoid factor amount	[182]
Resveratrol	Rats with induced RA	10 mg/kg	↓ Wnt5a, MAPK3, Src kinase, and STAT3 levels	[279]
Resveratrol	Rats with induced RA	10 mg/kg	↓ IL-6 and TNF-α levels, atrial apoptosis and fibrosis, and activate the AMPK/PGC-1α pathway	[280]
Resveratrol	Rats with induced RA	10 mg/kg	↓ serum rheumatoid factor, MMP-3, cartilage oligomeric matrix protein, IgG, antinuclear antibody, TNF-α, MPO, C-reactive protein and MDA ↑ IL-10 and glutathione	[281]
Resveratrol	Rats with induced RA	50 mg/kg	↓ paw swelling, TNF-α, IL-1β, TBARs, and NOx Suppress NF-κB p65 expression	[282]
Resveratrol	Rabbit inflammatory RA model	10 μMol/kg	↓ inflammatory responses Prevent the loss of matrix proteoglycan content in the cartilage in	[283]
Resveratrol	Murine collagen-induced arthritis	15 and 20 mg/kg	Inhibition of Th17 and B-cell function	[284]

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Resveratrol	Rats with bovine type-II collagen-induced arthritis	400 g/kg/bw	↓ oxidative stress and inflammation, and MDA levels ↑ serum superoxide dismutase Suppress MAPK signalling pathways, and angiogenesis	[250]
*R*esveratrol	Adjuvant arthritis rat model	45 mg/kg	↓ store-operated Ca^{2+} entry ↑ apoptosis Interference on ORAI1-STIM1 complex	[285]
Resveratrol	Rats with induced RA	12.5 mg/kg	Induce the noncanonical autophagy pathway ↓ p62 expression, caspase-3 expression and poly(ADP-ribose) polymerase, IL-1β, C-reactive protein, and prostaglandin E2,and NF-κB synovial tissue expression	[286]
Resveratrol	Rats with induced RA	12.5 mg/kg	↓ PCNA, CD68, CD3, monocyte chemoattractant protein-1 staining, cytokine-induced neutrophil chemoattractant-1 and the level of the marker of DNA damage, 8-oxo-7,8-dihydro-2'-deoxyguanine	[287]
Resveratrol	Collagen-induced arthritis rat model	2.5 and 10 mg/kg	Suppress MMP1 and MMP13 amounts	[246]
Resveratrol	Adjuvant arthritis rats	10 and 50 mg/kg	↓ the proliferation of concanavalin A-stimulated spleen cells, articular cartilage degeneration with synovial hyperplasia and inflammatory cell infiltration Suppress the production of COX-2 and PGE2	[288]
Resveratrol	Rats with induced RA	10 mg/kg	Alleviates adjuvant arthritis-interstitial lung disease	[289]
Resveratrol	Rats with induced RA	10 mg/kg	Prevent the production of pro-inflammatory via modulating JAK/STAT/RANKL signalling pathway Ameliorate fibrosis via autophagy-lysosome pathway	[186]
Resveratrol combined with methotrexate loaded-nanoemulsion	Rats with induced RA	Not mentioned	↓ inflammation Better anti-arthritic effects potentiated by resveratrol	[290]

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QRu-PLGA-DS nanoparticles carried resveratrol	Arthritic rats	Not mentioned	Improvements the water solubility and targeting the effectiveness of this compound Ameliorate anti-inflammatory effects ↑ M2 type macrophages transformation ↓ the recruitment of the M1 type macrophages	[291]
Ellagic acid	Arthritic rats	5, 50 and 100 mg/kg	↓ oxidative stress and inflammation ↑ serum superoxide dismutase *S*uppress MAPK signalling pathways, angiogenesis *and* MTA1/HDAC1-mediated Nur77 deacetylation	[266]
Ellagic acid	Arthritic rats	25 mg/kg	↓ articular edema, NF-*k*B, and neutrophil elastase, neutrophil extracellular traps *I*nterfer*ence on* TLR-4, peptidyl arginine deiminase 4 enzyme and COX-2	[292]
Epigallocatechin gallate	Rats with induced RA	10 mg/kg	Ameliorate RA symptoms ↓ histological scores in arthritic mice, as well as reduce IgG2a antibodies Suppress T cell proliferation and relative frequencies of CD4 T cells, CD8 T cells and B cell subsets ↑ the frequency of $CD4^+$-$Foxp3^+$ Treg cells and indoleamine-2,3-dioxygenase expression by $CD11b^+$ dendritic cells, NF-kB, Nrf-2 and heme oxygenase-1	[293]
Epigallocatechin gallate	Collagen-induced arthritis rat model	50 mg/kg	↓ TNF-α, IL-17, Nrf-2 and MDA levels ↑ heme oxygenase-1, superoxide dismutase, catalase and glutathione peroxidase levels	[188]
Epigallocatechin gallate	Rats with induced RA	10 mg/kg	↓ neuroinflammation, namely by activating caspase-3	[294]
Epigallocatechin gallate	Mice with collagen-induced arthritis	50 mg/kg	↓ arthritis index Protective effects against joint destruction Inhibition of osteoclastogenesis and TH17 cells activation ↑ the number of Treg cells	[295]

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Extracellular vesicles-encapsulated epigallocatechin gallate	Rats with induced RA	Not mentioned	Downregulate the expression of hypoxia-inducible factor 1-α Inhibition apoptosis of chondrocytes Promote the recovery of type II collagen ↓ joint swelling	[296]
Epigallocatechin	Arthritic rats	Not mentioned	↑ reduced elastic modulus, hardness and stiffness in cartilage	[297]
Epigallocatechin	Rats with induced RA	10 mg/kg	*Prevent* cartilage destruction in at, by imbibing myeloperoxidase activity. Moreover,	[298]
Green tea	Rats with induced RA t	2-12 g/L	↓ RA severity and IL-17 levels ↑ IL-10 levels Suppress the anti-Bhsp65 antibody response	[299]
Tinospora cordifolia	Rats with induced RA	150 mg/kg	↓ erythema, paw edema, hyperplasia, IL-6, TNF-α, IL-17, NO and PGE2 levels phosphorylation of STAT3 and the expression of VEGF	[273]
Kalpaamruthaa	Rats with induced RA	150 mg/kg	↓ oxidative stress, myeloperoxidase and lipid peroxide and increase the activity of enzymic and non-enzymic antioxidants	[300]
Ribes orientale	Sprague Dawley rats with induced RA	50, 100, 200 mg/kg	↓ paw volume/diameter, and PGE2, COX-2, IL-1β, IL-6, NF-*k*B and TNF-α levels ↑ IL-4 and IL-10	[183]
Chebulanin	Collagen-induced arthritis mouse model	80 mg/kg	suppress the progression and development of RA ↓ arthritis severity scores, paw swelling and joint destruction, IL-6 and TNF-α amounts, excised phosphorylated (p)-p38 and p-p65, phosphorylated-c-JUN N-terminal kinase and phosphorylated NF-κB and inhibitor alpha	[185]
Punicalagin	Rats with induced RA	50mg/kg/	Prevent the translocation of p-65 Avoid the phosphorylation of IkK and Ik Bα, Modulate NF-kB pathway	[244]

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			↓ TNFα, IL-6, CD86, CCR7, CD40 and MHC II expression, Th1, Th17 and Th17/Th1-like ↑ IL-10 expression Suppress dendritic cells migration, which, in turn Promote the generation of Tregs via regulation of dendritic cells maturation	
Syringaldehyde	Rats with induced RA	10, 25, 50 mg/kg	Alleviate paw and joint edema ↓ TNF-α and IL-6 levels ↑ IL-10	[245]
Syringaldehyde	Rats with induced RA	100 and 200 mg/kg	↓ IL-6 and TNF-α levels	[301]
Clitoria ternatea flower petals and its major compound, quercetin-3ß-D-glucoside	Rats with induced RA	50 mg/kg *Clitoria ternatea* flower petals, and 2.5 mg/kg of quercetin-3β-D-glucoside	↓ MPO activity and pro-inflammatory cytokines, chemokines, RNOS, and TNFR1, TLR2, iNOS, COX-2 and MMP-2 expression levels	[302]
Berberis orthobotrys Bien ex Aitch	Rats with induced RA	150 mg/kg	Protection against arthritic lesions, oxidative damage and body weight alterations* Ameliorated altered hematological parameters, rheumatoid factor Contributed to positively modified radiographic and histopathological changes	[303]
Diospyros malabarica (Desr.) Kostel fruits	Rats with induced RA	250, 500 and 750 mg/kg	↑ anti-inflammatory enzymes ↓ anti-inflammatory enzymes	[304]
ρ-Coumaric acid	Rats with induced RA	100 mg/kg	Suppress paw edema and body weight loss ↓ cartel	[272]
ρ-Coumaric acid	Rats with induced RA	100 mg/kg	↓ age, bone erosion, TNF-α, IL-1β, IL-6, IL-17 and MCP-1, and the expression of RANKL and TRAP, *i*NOS and COX-2, JNK, p-JNK, and ERK1/2 Regulate the RANKL/OPG imbalance Inhibition the RANKL-induced NFATc-1 and c-Fos expression	[192,305]

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Chlorogenic acid	Rats with induced RA	10 mg/kg	Attenuate liposaccharide-induced bone loss of rat femurs	[271]
Theaflavin-3, 3'-digallate	Collagen-induced RA mouse model	10 mg/kg	↓ IL-1β, TNF-α, IL-6, as well as MMP-1, MMP-2, and MMP-3 amounts Inhibition the activation of NF-kB and the phosphorylation of P38, JNK2, and ERK	[184]
Cinnamtannin D1	Rats with induced RA	50 mg/kg	Alleviate the severity of RA ↓ clinical scores and paw swelling, inflammatory cell infiltration, cartilage damage in the joints, and IL-17, IL-6, and IL-1β levels, and the frequency of Th17 cells ↑ TGF-β and IL-10 levels and the frequence of Treg cells Inhibition of aryl hydrocarbon receptor expression and phospho-STAT3/RORγt	[306]
Cinnamon barks	Mice with induced RA	200 mg/kg	↓ paw volume, weight loss, and IL-2, IL-4 and IFNγ levels	[307]
N-feruloylserotonin	Rats with induced RA	3mg/kg	↓ C-reactive protein, the activity of LOX, as well as mRNA transcription of TNF-α, iNOS IL-1β and IL-1β mRNA expression	[308]
Extra virgin olive oil	Mice with collagen-induced RA	100 and 200 mg/kg	↓ inflammatory markers, joint edema, cell migration, cartilage degradation and bone erosion, and also reducing COX-2 and microsomal prostaglandin E synthase-1 expression Inhibition c-Jun N-terminal kinase, p38, signal transducer and activator of transcription-3	[309]
Hydroxytyrosol acetate	Mice with collagen-induced RA	0.05%	↓ IgG1 and IgG2a, COMP, MMP-3, TNF-α, IFN-γ, IL-1β, IL-6 and IL-17A, and MAPKs JAK/STAT and NF-κB pathways ↑ Nrf-2 and heme oxygenase-1	[310]
mangiferin	Mice with induced RA	50, 100 and 400 mg/kg	Inhibition of mRNA expression of cytokine genes in thymus and spleen, and also NF-κB and activating ERK1/2 ↓ IL-1β, IL-6, TNF-α, and RANKL	[311]

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Sarcococca saligna	Rats with induced RA	250 mg/kg	↓ IL-1β, IL-6, COX-2, prostaglandin E2, TNF-α and NF-κB levels, arthritic index and paw inflammation ↑ IL-4 and IL-10 levels	[190]
Curcumin	Rats with induced RA	10 mg/kg	↓ TNF-α and IL-1β	[312]
Dichrostachys cinerea fruits	Rats with induced RA	75.48 mg	↓ IL-1β, IL-6, TNF-α and cortisol levels, lipid peroxidation and NOx production	[313]
Circaea mollis Sieb. & Zucc. plant	Freund's complete adjuvant-induced arthritis model in rats	170-1350 mg/kg	↓ paw and inflammatory swelling, arthritis index, TNF-α and IL-1β levels ↑ IL-10 levels	[314]
Opuntia littoralis	Rats with induced RA	10 and 20 mg/100 g bw	↓ joint inflammation, paw swelling, edemas, MDA, and IL-1β, IL-6R, IL-6, IL-17, and IL-23, Ameliorated COX-2, NF-*k*B, STAT-3, PTEN, and RANKL expression Upregulate the expression of miR-28 and miR-199a	[193]
Antrocaryon micraster seeds	Rats with induced RA	25 and 100 mg/kg	↓ cachexia, paw edema, infiltration of inflammatory cells, pannus formation, and synovium damage	[315]
Dried plums	Transgenic mice with induced-RA	+ 20% dried plums in the normal diet	Protect articular cartilage ↓ synovitis, IL-1β, MCP1, MIP1α, MMP1 and MPP3, and RANKL expression Repress TNF-induced formation of osteoclasts and mRNA levels of cathepsin K and MMP9 Inhibition of NFATc1 expression and NF-κB activation	[316]
Opuntia monacantha	Rats with induced RA	750 mg/kg	↓ paw edema, arthritic score, rheumatoid factor, inflammation, COX-2, IL-6, TNF-α, IL-1, NF-kB, bone erosion and pannus formation Restore hemoglobin, white blood count and platelets parameters	[317]

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			↑ catalase and superoxide dismutase, IL-4 and IL-10 levels Inhibition of glutaminase 1 activity	
Solanum nigrum	Rats with induced RA	800 mg/kg	↓ paw edema Restore body weight, hematologic parameters, radiographic and histopathologic alterations	[318]
Quercetin and quercetin-loaded chitosan	Rats with induced RA	15 mg/kg quercetin and 10 and 20 mg/kg quercetin-loaded chitosan	↓ TNF-α and IL-6 The nanoencapsulation of quercetin enhances its efficacy	[319]
Grape polyphenols + propolis	Female rats with induced RA	1.25 g/kg grape polyphenols mixed with 1.25 g/kg propolis	↓ the intensity of cachexia and alleviate RA scores	[320]
Malvidin 3-*O*-β glucoside	Chronic rat adjuvant-induced arthritis with	125 mg/kg	↓ cachexia and arthritic paw scores	[100]
Phoenix dactylifera L. seeds	Rats with induced RA	30 mg/kg	↓ IL-1β levels, paw edema, erythrocyte sedimentation rate and C-reactive protein	[321]
Liposomal drug delivery system for morin	Rats with induced RA	Not mentioned	↓ TNF-α, IL-1β, IL-6, IL-17, RANKL, STAT-3, p-STAT-3, VEGF, iNOS and NF-*k*B-p65 ↑ osteoprotegerin and murin uptake by rats synovial and spleen macrophages	[189]
Clinical trials				
Low-calorie cranberry juice	500 mL/day	Women with RA	↓ anti-cyclic citrullinated peptide antibodies levels, pain intensity and swollen joints	[322]
Low-calorie cranberry juice + fish oil ω-3 fatty acids	500 mL/day of low-calorie cranberry juice	People with rheumatoid arthritis	↓ C-reactive protein, erythrocyte sedimentation rate and related-pain	[323]

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	with 3 g of fish oil ω-3 fatty acids			
Pomegranate extract	250 mg	RA patients	↓ swollen, pain intensity and tender joints, erythrocyte sedimentation rate and morning stiffness ↑ glutathione peroxidase	[324]
Resveratrol	1 g	RA patients	↓ joint swelling, tenderness, TNF-α, IL-6, protein C-reactive, MMP-3, erythrocyte sedimentation rate and undercarboxylated osteocalcin	[325]

↑: enhance; ↓ diminish; IL: interleukin; ROS: reactive oxygen species; RONS: reactive oxygen and nitrogen species; NO: nitric oxide; TNF: Tumor necrosis factor; MMP: matrix metalloproteinase; SIRT: sirtuin; MDA: malondialdehyde; iNOS: Inducible nitric oxide synthase; VEGF: Vascular endothelial growth factor; STAT: signal transducers and activators of transcription; RANKL: eceptor activator of nuclear factor kappa beta; RA: rheumatoid arthritis; NF-*k*B: nuclear factor kappa B; MPO: myeloperoxidase; COX: cyclooxygenase; JNK: c-Jun N-terminal kinase; ERK: ; BAX: Bcl-2 associated X protein; Bcl-2: B-cell lymphoma 2; MAPK *: mitogen-activated protein kinase; ERK: extracellular signal-regulated kinase.*

 doi:10.20944/preprints202404.0585.v1

1, 3 and 10 μg/mL Resveratrol also showed ability to reduce Sirt1 protein, MMP1 and MMP13 expression [246], and, at 20 μM, inhibits the phosphorylation and acetylation of p65, c-Jun, and Fos and reduced the binding to the COX-2 promoter, thereby attenuated the COX-2 expression in fibroblast-like synoviocytes [247]. In addition, this compound at 1-40 μM also showed ability to activate Nrf2-2, heme oxygenase-1, and Bcl-2/Bax, induce apoptosis, reduce Keap1 expression and reative oxigen species and malondialdehyde levels, block NF-κB p6 translocation, inhibit cell proliferation and migration on fibroblast-like synoviocytes, in a dose-dependent manner [248,249]. Moreover, Yang and co-workers [250] demonstrated that 25 and 50 μmol/L resveratrol can reduce hypoxia-inducible factor-1α and activated phosphorylation of p38 MAPK and c-Jun N-terminal kinase in IL-1β-stimulated RSC-364 cells, as well as arrest these cells at G0/G1 cell-cycle and enhance their apoptosis. Similar data was reported by Tian et al. [251,252], who also verified that resveratrol can also interfere PI3K/Akt/BAD signalling pathway, which consequently, also promotes the inhibition of cells growth and apoptosis. In addition to that, 20 μM resveratrol can also interfere not only with PI3K/AKT but also with MEK/ERK pathway, and thus, inducing FOXO transcriptional activity and inhibiting cell migration and capillary tube formation in human umbilical vein endothelial cells, preventing angiogenesis [253]. On the other hand, Li et al. [254] reported that 50 μM resveratrol can block fibroblast-like synoviocytes in RA cells at the G2/M stage and reduce TNF-α levels and S phase cells ratio via promoting the serine-threonine kinase-p53 axis, and autophagy, which, subsequently, consequently lead to cells apoptosis. Moreover, 100 and 200 μM resveratrol, also showed ability to reduce the viability of human RA synovial MH7A cells, by stimulating H2A.X phosphorylation and consequent apoptosis events, disrupte mitochondrial membrane potentials and stimulated cytochrome c release from the mitochondria to the cytosol, activate caspase-3 and caspase-9 but not caspase-8, upregulated the expression of the NAD-dependent deacetylase sirtuin (SIRT) 1 mRNA and downregulated the expression of the Bcl-X(L) mRNA, and hence, suppressing synovial cells hyperplasia [255]. The capacity of resveratrol to activate caspase-3, and consequent inhibits the proliferation of synoviocytes and induces cell apoptosis in synoviocytes in RA has already been reported by Tiang et al. [256]. Furthermore, Wang and colleagues revealed that 25-200 μM of this compound can also reduce mitochondrial reactive oxygen species, Bcl-2 associated X protein (Bax) and increase B-cell-lymphoma-2 (Bcl-2 levels) and apoptotic cells, namely by regulating the expression of mitochondrial superoxide dismutase [257]. On the other hand, a dose of 100 μM resveratrol reduces the expression of MMP-1, MMP-3, MMP-9, RANKL, osteoprotegrin [258], and TNF-α by interfering with sirtuin1/cortistatin pathway [259], as well as increase the expression of genes involved in mitosis, cell cycle, chromosome segregation and apoptosis in RA fibroblast-like synoviocytes [260]. Similar data was obtained by Lu and co-workers [261] who also verified that resveratrol can diminish the expression of IL-1, IL-6, IL-8 and TNF-α, raise the expression of IL-10, as well as the administration of resveratrol together with 5 μM hydrogen peroxide induce fibroblast-like synoviocytes apoptosis probably via mitochondrial dysfunction and endoplasmic reticulum stress. Resveratrol can also diminish urban particulate matter-induced COX-2/PGE2 release in human fibroblast-like synoviocytes by inhibiting the activation of NADPH oxidase/ROS/NF-κB [262]. Finally, 1, 2, 3 and 5 μM resveratrol can mediated SIRT-1 interactions with p300, modulating RANKL activation of NF-kB signaling, inhibiting osteoclastogenesis, and thus, preventing bone loss in bone-derived cells [263].

In addition, it was also already reported that the combination of 25 μM resveratrol with 0.5 μg/mL methotrexate significantly reduced monocyte chemoattractant protein 1 levels in synovial mononuclear cells from RA patients [264].

1, 10 and 100 μM purified grape-derived compounds, whose main compound is malvidin 3-O-β glucoside, showed capacity to inhibit the expression of TNF-α, IL1, IL-6 and iNOS genes from secretion-activated macrophages of human peripheral blood mononuclear cells [100].

1, 1 and 10 μg/mL 1,2,3,4,6-penta-O-galloyl-beta-D-glucose, 1,2,6-tri-O-galloyl-beta-D-allopyanose, and 1,2,3,6-tetra-O-galloyl-beta-D-allopyranose gallotannins also showed potential to downregulate NF-kB expression, in a dose dependent in human mast cells [265].

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Focusing on phenolic acids, 10, 25, 50 and 100 μM ellagic acid already showed potential to reduce IL-6, IL-1β, malondialdehyde and TNF-α and raise superoxide dismutase and apoptosis in fibroblast-like synoviocyte MH7A cells pre-treated with TNF-α to induce inflammation by inhibiting metastasis-associated gene 1, which is a component of NF-kB signalling, and a upstream modulator of inflammation and immunologic responses [266]. On the other hand, 0.1 and 1 μM gallic acid increase caspase-3 activity, regulate Bcl-2, Bax, p53 and pAkt productions and reduce IL-1β, IL-6, CCL-2/MCP-1, CCL-7/MCP-3, COX-2, and MMP-9 from on fibroblast-like synoviocytes from patients with RA [267]. More recently, it was reported rosmarinic acid nanoparticles showed a favourable capability in scavenging reactive oxygen and nitrogen species and pro-inflammatory cytokines produced by macrophages [191]. ϱ-Coumaric acid encapsulated with mannosylated liposomes showed similar effects, as well as ability to inhibit the osteoclasts differentiation and downregulate the expression of MMP-9 and NFATc1 [268]. Moreover, 25-300 μM ferulic acid showed ability to reduce IL-17-levels in RA fibroblast-like synoviocytes, thanks to its ability to inhibit IL-17/IL-17RA/STAT-3 signalling cascade [269]. In addition, this acid at doses of 25, 50 and 100 μM can attenuate RANKL-induced osteoclast differentiation, and consequently decrease bone resorption activity by downregulating NFATc1, c-Fos, TRAP, Cathepsin K and MMP-9 levels in RAW 264.7 macrophages [270]. On the other hand, 10-50 μg/mL chlorogenic acid can inhibit osteoclast differentiation and bone resorption by down-regulating RANKL on activated T cells c1, as well as by suppressing mRNA expression of NFATc1, TRAP and OSCAR [271].

Tea polyphenol carrier-enhanced dexamethasone showed ability to reduce inflammatory mediators in the LPS/INF-γ-induced inflammatory cell models, including umbilical vein endothelial, murine fibroblast cells L929 and murine macrophage RAW 264.7 cells [272]. Tinospora cordifolia also showed anti-inflammatory effects on lypossacharide-stimulated RAW 264.7 cells, by reducing IL-6, TNF-α, PGE2, and nitric oxide levels and iNOS and COX expression via modulation of JAK/STAT pathway [273]. On the other hand, 100-200 μM blueberry polyphenols can reduce TNF-α, IL-1β, MMP3 and NF-kB levels on HIG-82 rabbit synoviocytes previous stimulated with TNF-α [274]. Moreover, 10 and 20 μg/mL cocoa polyphenols can suppress TNF-α-induced vascular endothelial growth factor expression by inhibiting phosphoinositide 3-kinase (PI3K) and mitogen-activated protein kinase kinase-1 (MEK1) activities in mouse epidermal cells [275]. 5-80 μM Catechin-7,4'-O-digallate from Woodfordia uniflora can also regulate NF-kB signalling pathway in mouse macrophages and reduce IL-6 and IL-1β levels [276]. On the other hand, Salacia reticulata leaves showed capacity to inhibit MTS-C H7 cells proliferation (IC_{50} score of ~850 μg/mL) [277].

In Vivo Studies

On the other hand, in RA-mice models, 50, 100 and 150 mg/kg/day slibinin showed ability to diminish IL-1β, IL-6 and TNF-α levels, and joint inflammation [237].

Resveratrol revealed to be a promising strategy for attenuating RA in mice model. In fact, a 12-day treatment with 5 mg/kg, 15 mg/kg and 45 mg/kg resveratrol can reduce the abnormal proliferation of fibroblast-like synoviocytes, swelling degree of the paw and malondialdehyde levels, and increase superoxide dismutase activity, and glutathione peroxidase and glutathione reductase ratio [278]. Furthermore, this compound at 10 mg/kg, also showed ability to reduce the progression of periodontitis and rheumatoid factor amount [182], Wnt5a, MAPK3, Src kinase, and STAT3 levels [279], diminish IL-6 and TNF-α levels, atrial apoptosis and fibrosis, and activate the AMPK/PGC-1α pathway [280], as well as decreased to about 37, 59, 44, 70, 5, 30, 23, 33 and 28% serum rheumatoid factor, MMP-3, cartilage oligomeric matrix protein, IgG, antinuclear antibody, TNF-α, myeloperoxidase, C-reactive protein and malondialdehyde, respectively, and enhance to about 225 and 273% IL-10 and glutathione, respectively in RA-rats [281]. Furthermore, 50 mg/kg resveratrol can diminish paw swelling, TNF-α, IL-1β, TBARs, and NOx, namely by suppressing NF-κB p65 expression [282], while 10 μMol/kg can reduce inflammatory responses and prevent the loss of matrix proteoglycan content in the cartilage in a rabbit inflammatory arthritis model [283]. Moreover, a 10-day treatment with 15 and 20 mg/kg resveratrol modulates murine collagen-induced arthritis by inhibiting Th17 and B-cell function [284]. In accordance with other studies, Yang et al. [250] also

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revealed 400 g/kg/bw resveratrol diminishes oxidative stress and inflammation, by raising serum superoxide dismutase and reducing malonaldehyde, and suppress MAPK signalling pathways, and angiogenesis in rats with bovine type-II collagen-induced arthritis. Similar results were observed in arthritic rats treated with 5, 50 and 100 mg/kg ellagic acid for 21 days, where ellagic acid also showed capacity to suppress MTA1/HDAC1-mediated Nur77 deacetylation [266]. Furthermore, 25 mg/kg of this compound can also decrease articular edema, NF-kB, and neutrophil elastase, and hence, diminishing neutrophil extracellular traps, on RA rats namely by interfering with TLR-4, peptidyl arginine deiminase 4 enzyme and COX-2 [292]. 45 mg/kg Resveratrol can also reduce store-operated Ca^{2+} entry and enhance the apoptosis in adjuvant arthritis rat model via targeting ORAI1-STIM1 complex [285]. Additionally, Fernández-Rodríguez et al. [286] reported that 12.5 mg/kg/day resveratrol can also induce the noncanonical autophagy pathway, reduces p62 expression, caspase-3 expression and poly(ADP-ribose) polymerase, IL-1β, C-reactive protein, and prostaglandin E2, as well as NF-κB synovial tissue expression, which is correlated with p62 expression [286], as well as diminish PCNA, CD68, CD3, monocyte chemoattractant protein-1 staining, cytokine-induced neutrophil chemoattractant-1 and the level of the marker of DNA damage, 8-oxo-7,8-dihydro-2'-deoxyguanine in RA rats [287]. 2.5 and 10 mg/kg/day resveratrol can also display ability to suppress MMP1 and MMP13 amounts in a collagen-induced arthritis rat model [246], while 10 and 50 mg/kg resveratrol can reduce the proliferation of concanavalin A-stimulated spleen cells, articular cartilage degeneration with synovial hyperplasia and inflammatory cell infiltration, namely by suppressing the production of COX-2 and PGE2 in adjuvant arthritis rats [288]. 10 mg/kg/day Resveratrol alleviates adjuvant arthritis-interstitial lung disease in rats with induced RA, namely by preventing the production of pro-inflammatory via modulating JAK/STAT/RANKL signalling pathway [289], as well as ameliorate fibrosis in rats with induced-RA via autophagy-lysosome pathway [186].

More recently, and to improve resveratrol's bioavailability and effectiveness, it was shown that its combination with methotrexate loaded-nanoemulsion in a transdermal delivery system resulted in a reduction of inflammation by 78.76% and better anti-arthritic effects [290]. Moreover, the nanocarrier QRu-PLGA-DS nanoparticles effectively improved the water solubility and targeting the ability of this compound to reverse the M1 to the M2 type macrophages and ameliorate its anti-inflammatory effects in arthritic rats; in addition, the accumulation of nanoparticles in the lesion area with an exogenous stimulus, significantly raise the transformation of the M2 type macrophages and decrease the recruitment of the M1 type macrophages [291].

Regarding epigallocatechin gallate, 10 mg/kg of this one can ameliorate clinical symptoms and reduce histological scores in arthritic mice, as well as reduce IgG2a antibodies, suppress T cell proliferation and relative frequencies of CD4 T cells, CD8 T cells and B cell subsets, including marginal zone B cells, T1 and T2 transitional B cells, and increase the frequency of $CD4^{+}$-$Foxp3^{+}$ Treg cells and indoleamine-2,3-dioxygenase expression by $CD11b^{+}$ dendritic cells, NF-kB, Nrf-2 and heme oxygenase-1 [293]. On the other hand, in collagen-induced arthritis rat model, 50 mg/kg/day epigallocatechin gallate also revealed capacity to diminish TNF-α, IL-17, Nrf-2 and malondialdehyde levels and improve heme oxygenase-1, superoxide dismutase, catalase and glutathione peroxidase levels [188]. Moreover, this one can also reduce neuroinflammation in RA rats after 2 months of treatment, namely by activating caspase-3 [294]. Moreover, 50 mg/kg epigallocatechin gallate already showed ability to decrease arthritis index, show protective effects against joint destruction in mice with collagen-induced arthritis, inhibit osteoclastogenesis and TH17 cells activation, and increase the number of Treg cells [295]. On the other hand, the administration of extracellular vesicles-encapsulated epigallocatechin gallate for cartilage repair in rat arthritis reduced down-regulate the expression of hypoxia-inducible factor 1-α, inhibit apoptosis of chondrocytes, promote the recovery of type II collagen and reduce joint swelling in rheumatoid rats by approximately 39.5% [296]. In addition, the nanoindentation of epigallocatechin significantly increases reduced elastic modulus (57.5%), hardness (83.2%), and stiffness (17.6%) in cartilage of arthritic rats [297]. This one also showed capability of preventing cartilage destruction in rats with induced-RA at 10 mg/kg, by imbibing myeloperoxidase activity [298].

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Regarding green tea, it was also reported that rats with induced-RA that ingest 2-12 g/L in drinking water for 1-3 weeks showed significant reductions in RA severity, lower levels of IL-17 and higher levels of IL-10, and this is probably due to the capacity of green tea polyphenols to suppress the anti-Bhsp65 antibody response [299].

150 mg/kg Tinospora cordifolia reduced erythema, paw edema, hyperplasia, IL-6, TNF-α, IL-17, nitric oxide and PGE2 levels, as well as phosphorylation of STAT3 and the expression of VEGF [273].

150 mg/kg/bw Kalpaamruthaa, a modified indigenous Siddha preparation constituting Semecarpus anacardium nut milk extract, Emblica officinalis and honey also showed potential to reduce oxidative stress, myeloperoxidase and lipid peroxide and increase the activity of enzymic and non-enzymic antioxidants in arthritic rats [300].

In addition, 50, 100, 200 mg/kg doses of Ribes orientale aqueous ethanolic extract (30:70) showed potential to reduce paw volume/diameter, and PGE2, COX-2, IL-1β, IL-6, NF-kB and TNF-α levels, and enhance IL-4 and IL-10 contents in Sprague Dawley rats with induced RA [183], Additionally, 80 mg/kg daily of chebulanin for 3 weeks significantly suppressed the progression and development of RA in collagen-induced arthritis mouse model, by decreasing the arthritis severity scores, attenuating paw swelling and joint destruction, and reducing IL-6 and TNF-α amounts, excised phosphorylated (p)-p38 and p-p65, phosphorylated-c-JUN N-terminal kinase, and phosphorylated NF-κB inhibitor alpha, but without effects on extracellular-signal-regulated kinase levels [185].

50mg/kg/d Punicalagin also showed capacity to prevent the translocation of p-65 and avoid the phosphorylation of IkK and Ik Bα, by modulating NF-kB pathway in arthritic rats, as well as to reduce TNFα, IL-6, CD86, CCR7, CD40 and MHC II expression, raise IL-10 expression and suppress dendritic cells migration, which, in turn, causes diminish the differentiation of Th1, Th17 and Th17/Th1-like and promoting the generation of Tregs via regulation of dendritic cells maturation [244]. 10, 25, 50 mg/kg Syringaldehyde also showed ability to alleviate paw and joint edema, reduce TNF-α and IL-6 levels and increase the level of IL-10 in arthritic rats' serum [245]. Lower levels of IL-6 and TNF-α were also obtained by Toy and colleagues at doses of 100 mg/kg and 200 mg/kg/bw [301]. Furthermore, 50 mg/kg Clitoria ternatea flower petals and 2.5mg/kg of its major compound, which is quercetin-3ß-D-glucoside showed ability to reduce MPO activity and low pro-inflammatory cytokines, chemokines, reactive oxygen and nitrogen species, and TNFR1, TLR2, iNOS, COX-2 and MMP-2 expression levels in rats with RA [302]. Similar effects were observed by 150 mg/kg Berberis orthobotrys Bien ex Aitch, which also offered protection against arthritic lesions, oxidative damage and body weight alterations, ameliorated altered hematological parameters, rheumatoid factor and contributed to positively modified radiographic and histopathological changes [303]. 250, 500 and 750 mg/kg Diospyros malabarica (Desr.) Kostel fruits also showed capacity to raise anti-inflammatory enzymes and diminish the anti-inflammatory ones in RA rat model [304].

On the other hand, the daily administration of 100 mg/kg daily ϱ-coumaric acid for 2 weeks showed remarkable capacity to suppress paw edema, body weight loss, curtails cartel [272], age, bone erosion, TNF-α, IL-1β, IL-6, IL-17 and MCP-1 quantities in serum and ankle joint of arthritic rats, as well as the expression of RANKL and TRAP, iNOS and COX-2, JNK, p-JNK, and ERK1/2., namely by regulating the RANKL/OPG imbalance and inhibit the RANKL-induced NFATc-1 and c-Fos expression [192]. Similar data was reported by Pragasam and colleagues [305]. Focusing on chlorogenic acid, this one at 10 mg/kg can attenuate liposaccharide-induced bone loss based on micro-computed tomography and histologic analysis of femurs from arthritic rats [271].

10 mg/kg Theaflavin-3, 3'-digallate administrated three times per week 9 continuous weeks also showed capability of reducing the expression of IL-1β, TNF-α, IL-6, as well as MMP-1, MMP-2, and MMP-3 amounts in the synovium of collagen-induced arthritis mouse model, chiefly by inhibiting the activation of NF-kB and the phosphorylation of P38, JNK2, and ERK [184]. Moreover, 50 mg/kg cinnamtannin D1, a polyphenolic compound isolated from Cinnamomum tamala, alleviates the severity of RA, affording reduced clinical scores and paw swelling, and reduced inflammatory cell infiltration, cartilage damage in the joints, IL-17, IL-6, and IL-1β, and enhanced TGF-β and IL-10 levels, as well as reduce the frequency of Th17 cells and enhance the frequency of Treg cells, namely by its potential to inhibit aryl hydrocarbon receptor expression and phospho-STAT3/RORγt [306].

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On the other hand, 200 mg/kg cinnamon barks reduce paw volume, weight loss, and, IL-2, IL-4 and IFNγ in RA mice model [307].

3mg/kg/day orally N-feruloylserotonin, a natural polyphenol that belongs to indole hydroxycinnamic acid amides, reduced C-reactive protein in plasma and the activity of LOX in the liver rats, as well as mRNA transcription of TNF-α and iNOS in the liver and IL-1β in plasma and IL-1β mRNA expression in the liver and spleen of arthritic rats [308].

Moreover, 100 and 200 mg/kg extra virgin olive oil showed capability to decrease inflammatory markers, joint edema, cell migration, cartilage degradation and bone erosion in collagen-induced arthritis model mice, namely by inhibiting c-Jun N-terminal kinase, p38, signal transducer and activator of transcription-3, as well as reducing COX-2 and microsomal prostaglandin E synthase-1 expression [309]. Furthermore, 0.05% hydroxytyrosol acetate, a polyphenol present in extra virgin olive oil showed ability to diminish IgG1 and IgG2a, COMP, MMP-3, TNF-α, IFN-γ, IL-1β, IL-6 and IL-17A, and MAPKs JAK/STAT and NF-κB pathways and enhance Nrf-2 and heme oxygenase-1 in mice with collagen-induced arthritis [310].

In addition, 50, 100 and 400 mg/kg mangiferin inhibits mRNA expression of cytokine genes in thymus and spleen of mice with induced-arthritis and lead to decreased serum levels of IL-1β, IL-6, TNF-α, and RANKL by downregulating NF-κB and activating ERK1/2 [311].

250 mg/kg Sarcococca saligna plant also showed ability to diminish IL-1β, IL-6, COX-2, prostaglandin E2, TNF-α and NF-κB levels, arthritic index and paw inflammation, and enhance the expression of IL-4 and IL-10 [190]. On the other hand, 10 mg/kg curcumin showed similar effects as positive control methotrexate (0.5 mg/kg) in reducing TNF-α and IL-1β in both synovial fluid and blood serum of arthritic rats [312]. Aqueous extracts of Dichrostachys cinerea fruits at doses of 150.96 mg GAE/g and 75.48 mg GAE/g reduced IL-1β, IL-6, TNF-α and cortisol levels, lipid peroxidation and NOx production [313]. In addition, 170-1350 mg/kg Circaea mollis Sieb. & Zucc. plant can also reduce paw and inflammatory swelling, arthritis index, TNF-α and IL-1β, and increase the production of serum IL-10 in Freund's complete adjuvant-induced arthritis model in rats [314]. 10 and 20 mg/100 g bw Opuntia littoralis also revealed potential to reduce joint inflammation, paw swelling, edemas, MDA, and IL-1β, IL-6R, IL-6, IL-17, and IL-23, and ameliorated COX-2, NF-kB, STAT-3, PTEN, and RANKL expression, namely by up-regulating the expression of miR-28 and miR-199a [193]. Furthermore, 25 and 100 mg/kg Antrocaryon micraster seed extract also showed capacity to diminish cachexia, paw edema, infiltration of inflammatory cells, pannus formation, and synovium damage in rats with induced RA [315]. Moreover, the addition of 20% dried plums in the normal diet of transgenic mice with induced-RA showed notable protective effects in protecting articular cartilage, reducing synovitis, IL-1β, MCP1, MIP1α, MMP1 and MPP3, and RANKL expression and repressing TNF-induced formation of osteoclasts and mRNA levels of cathepsin K and MMP9 by inhibiting nuclear factor of activated T-cells, cytoplasmic 1 (NFATc1) expression and NF-κB activation [316]. On the other hand, 750 mg/kg Opuntia monacantha showed effectiveness in reducing paw edema, arthritic score, rheumatoid factor, inflammation, COX-2, IL-6, TNF-α, IL-1, NF-kB, bone erosion and pannus formation, restore hemoglobin, white blood count and platelets parameteres and increase catalase and superoxide dismutase levels, and enhance IL-4 and IL-10, namely by its potential to inhibit glutaminase 1 activity in a RA rat model [317]. In addition, 800 mg/kg Solanum nigrum also showed effectiveness in reducing paw edema, and restoring body weight, hematologic parameters, radiographic and histopathologic alterations towards normal in different RA rat models [318].

In addition, 15 mg/kg quercetin and 10 and 20 mg/kg quercetin-loaded chitosan showed capacity to reduce TNF-α and IL-6, being observed that the nanoencapsulation of quercetin is an added value to improve its efficacy in rats with induced RA [319]. 1.25 g/kg grape polyphenols mixed with 1.25 g/kg propolis showed potential to diminish the intensity of cachexia and alleviate RA scores in RA female rats [320]. Reduced cachexia and arthritic paw scores were also reported by Decendit [100] who treated chronic rat adjuvant-induced arthritis with 125 mg/kg malvidin 3-O-β glucoside.

Phoenix dactylifera L. seeds can diminish IL-1β levels, paw edema, erythrocyte sedimentation rate and C-reactive protein in rats [321].

 doi:10.20944/preprints202404.0585.v1

Finally, the liposomal drug delivery system for morin, a dietary polyphenol, showed capacity to ameliorate RA in rats, mainly by increasing its uptake by synovial and spleen macrophages, and reducing the mRNA expression and consequent production of TNF-α, IL-1β, IL-6, IL-17, RANKL, STAT-3, p-STAT-3, VEGF, iNOS and NF-kB-p65 and increase the expression of osteoprotegerin [189].

Clinical Trials

Regarding clinical trials, there were already related that 500 mL/day of low-calorie cranberry juice is able to attenuate RA symptoms in women with this disease after a 90-day treatment, by decreasing anti-cyclic citrullinated peptide antibodies levels, pain intensity and swollen joints; however, no inflammatory biomarkers were verified [322]. Additionally, the daily ingestion of 500 mL/day of low-calorie cranberry juice with 3 g of fish oil ω-3 fatty acids showed effectiveness in C-reactive protein, erythrocyte sedimentation rate and related-pain [323]. On the other hand, pomegranate extract (250 mg for 8 weeks), in addition to alleviating swollen, pain intensity and tender joints in RA patients, this one can also diminish erythrocyte sedimentation rate and morning stiffness and enhance glutathione peroxidase. No alterations were found in CRP, MDA and MMP3 levels [324]. Finally, a 1 g daily of resveratrol for 3 months [325] also showed effectiveness in reducing joint swelling and tenderness, as well as TNF-α, IL-6, protein C-reactive, MMP-3, erythrocyte sedimentation rate and undercarboxylated osteocalcin in RA patients of both genders [325].

5. Conclusions

In a general way, the present review is another evidence that supports the therapeutic effect of polyphenolics. Indeed, they seem to be a promising approach to boost immune system and contribute to a healthy status, mainly due to their capacity of counteract oxidative stress and ineract with inflammatory pathways. Given that, it is not surprising that their use as an adjuvant to conventional antirheumatic drugs is possible.

However, and although phenolics are easy to obtain and economical, most of them present poor bioavailability, and therefore, their encapsulation is an added value to increase their efficacy. In addition, their safety profile and successful clinical trials need to be more explored.

Author Contributions: Conceptualization, A.C.G., S.R. and R.F.; methodology, A.C.G., L.R.S.; software, A.C.G., S.R. and R.F..; validation, L.R.S.; formal analysis, A.C.G., S.R., R.F., L.R.S.; investigation, A.C.G., S.R., R.F. L.R.S.; resources, L.R.S.; data curation, A.C.G., S.R., R.F., L.R.S.; writing—original draft preparation, A.C.G.; writing—review and editing, L.R.S.; visualization, A.C.G., S.R., R.F. and L.R.S.; supervision, L.R.S.; project administration, L.R.S.; funding acquisition, L.R.S. All authors have read and agreed to the published version of the manuscript.

Funding: This work was partially supported by CICS-UBI (UIDP/00709/2020) and financed by the National Funds from Fundação para a Ciência e a Tecnologia (FCT) and CENTRO-04-3559-FSE-000162. This work was also financed by project PRR-C05-i03-I-000143 (RedFruit4Health), and by Fundação La Caixa and Fundação para a Ciência e Tecnologia (FCT) under the Programa Promove Project PD21-00023 (PharmaStar). The authors are also grateful to FCT, the Ministry of Science, Technology and Higher Education (MCTES), the European Social Fund (EFS), and the European Union (EU) for the PhD fellowship of Ana C. Gonçalves (2020.04947.BD).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflict of interest.

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 doi:10.20944/preprints202404.0585.v1