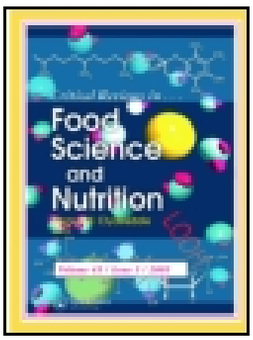


Critical Reviews in Food Science and Nutrition

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/bfsn20

Exploring the role of polyphenols in rheumatoid arthritis

Tapan Behl, Keshav Mehta, Aayush Sehgal, Sukhbir Singh, Neelam Sharma, Amirhossein Ahmadi, Sandeep Arora & Simona Bungau

To cite this article: Tapan Behl, Keshav Mehta, Aayush Sehgal, Sukhbir Singh, Neelam Sharma, Amirhossein Ahmadi, Sandeep Arora & Simona Bungau (2021): Exploring the role of polyphenols in rheumatoid arthritis, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2021.1924613

To link to this article: https://doi.org/10.1080/10408398.2021.1924613

Published online: 17 May 2021.

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
https://doi.org/10.1080/10408398.2021.1924613

Taylor & Francis
Taylor & Francis Group

REVIEW

Exploring the role of polyphenols in rheumatoid arthritis

Tapan Behl[a], Keshav Mehta[a], Aayush Sehgal[a], Sukhbir Singh[a], Neelam Sharma[a], Amirhossein Ahmadi[b], Sandeep Arora[a], and Simona Bungau[c]

[a]Chitkara College of Pharmacy, Chitkara University, Rajpura, Punjab, India; [b]Faculty of Pharmacy, Mazandaran University of Medial Sciences, Sari, Iran; [c]Department of Pharmacy, Faculty of Medicine and Pharmacy, University of Oradea, Oradea, Romania

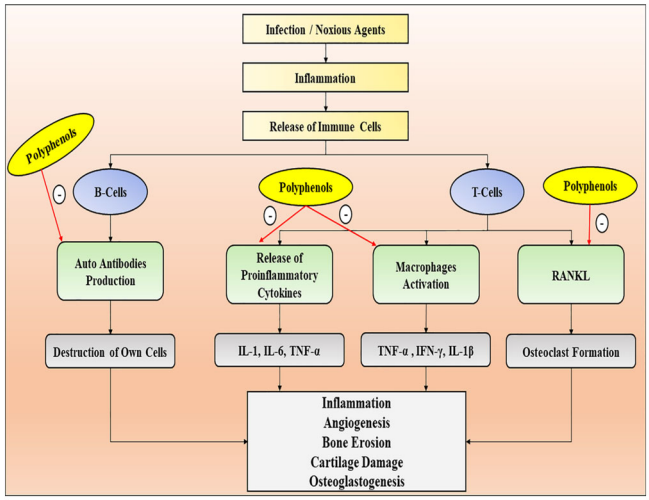
ABSTRACT

Rheumatoid arthritis (RA) is a chronic, inflammatory and autoimmune disorder which is mainly characterized by inflammation in joints, bone erosions and cartilaginous destruction that leads to joint dysfunction, deformation, and/or permanent functional impairment. The prevalence of RA is increasing, incurring a considerable burden on healthcare systems globally. The exact etiology of RA is unknown, with various pathways implicated in its pathophysiology. Non-steroidal anti-inflammatory drugs (NSAIDs) including celecoxib, diclofenac and ibuprofen, disease-modifying anti-rheumatic drugs (DMARD) including azathioprine, methotrexate and cyclosporine, biological agents including anakinra, infliximab, and rituximab and immunosuppressants are used for symptomatic relief in patients with RA, but these medications have severe adverse effects such as gastric ulcers, hypertension, hepatotoxicity and renal abnormalities which restrict their use in the treatment of RA; new RA treatments with minimal side-effects are urgently required. There is accumulating evidence that dietary polyphenols may show therapeutic efficacy in RA through their antioxidant, anti-inflammatory, apoptotic, and immunosuppressant activities and modulation of the tumor necrosis factor-α (TNF-α), interleukin (IL)-6, mitogen-activated protein kinase (MAPK), IL-1β, c-Jun N-terminal kinase (JNK), and nuclear factor κ light-chain-enhancer of activated B cell (NF-κB) pathways. While resveratrol, genistein, carnosol, epigallocatechin gallate, curcumin, kaempferol, and hydroxytyrosol have also been studied for the treatment of RA, the majority of data are derived from animal models. Here, we review the various pathways involved in the development of RA and the preclinical and clinical data supporting polyphenols as potential therapeutic agents in RA patients. Our review highlights that high-quality clinical studies are required to decisively establish the anti-rheumatic efficacy of polyphenolic compounds.

KEYWORDS

Polyphenol; rheumatoid arthritis; antioxidant; anti-inflammatory; apoptosis

GRAPHICAL ABSTRACT



Introduction

The immune system plays a vital role in the management of normal physiological and immunological functions of body. Any alteration in balance of immune system may leads to various life-threatening complications (Coussens and Werb 2002). The main function of our immune system is to protect our body from numerous diseases and infections that are caused by the various virus, bacteria and other causative

CONTACT Tapan Behl tapanbehl31@gmail.com Chitkara College of Pharmacy, Chitkara University, Rajpura, Punjab 140401 India.

agents. Although, in some specific conditions, the immune system may generate auto-antibodies against its own cells that results in destruction of own cells (autoimmune diseases). In such circumstances, there are failure in recognition between own cells and foreign cells (Khan et al. 2019; Rengasamy et al. 2019). The autoimmune diseases or disorders are mainly facilitate by the interaction between the complex inner and adaptive immunity with the specific genes. Among various types of arthritis such as osteoarthritis, rheumatoid arthritis and crystal-induced arthritis, rheumatoid arthritis (RA) is a most prevalent class that require a specific therapy due to obscure etiology and complex pathophysiology including several inflammatory factors (Donahue, Qu, and Genetos 2018; Oliviero et al. 2018; You et al. 2018). RA is a chronic, inflammatory and autoimmune disorder. Generally, it is characterized by destruction of cartilage, inflammation in synovium, prolonged stiffness, fatigue and swelling at specific and nonspecific sites (Gabriel 2001; Christman and Gu 2020; McInnes and Schett 2011; Nijhawan and Behl 2020). If this is not treated at early stage, these inflammatory responses are rapidly progressed and lead to irreversible or permanently destruction of joints (Liu et al. 2017; Singh et al. 2017). Some systemic and clinical manifestations including pulmonary serositis inflammation, skeletal disorders and vasculitis are also observed during the period of disease (Hughes, Ketheesan, and Haleagrahara 2017). According to a study, in 2015, more than 24.5 million of population were affected with RA. This number contains approximately 0.5–1% young persons in developed countries (Vos et al. 2016). The prevalence or occurrence of RA is more in European population (1%) as compared to African and Asian (< 0.5%). Countries including China, Pakistan, South Africa, Indonesia, the Philippines, Argentina and Nigeria are less prevalence with RA, compared to Western people. Data also suggested that the risk of RA in women is thrice in men (Hughes, Ketheesan, and Haleagrahara 2017; Oliviero et al. 2018). RA reduces the life span (about 20 years) and also decrease the quality of life of patients. Furthermore, it does not only affect the life style of patient but also show economic and social burden to the society. Although, people of all age group are influenced by RA but there are higher chances of occurrence of RA in 40–70 year age population. Therefore, it enhances the risk of morbidity and mortality (Khurana and Berney 2005). The exact etiology of RA is unknown due to its complexity. Recent studies reported that Prostaglandin (PG) E2, other inflammatory mediators including tumor necrosis factor (TNF)-α, interleukin (IL)-1β, are the major causes of initiation of disease and also play important role in the progression of RA (Li, Hsu, and Mountz 2012). Some recent data also revealed that receptor activator of nuclear factor κ B (RANK)/osteoprotegerin act as a prominent signal managing system for the metabolism of bone tissue and plays a pivotal role in osteoclastogenesis (Wada et al. 2006). Besides these proinflammatory cytokines, the overproduction of reactive oxygen species (ROS) may leads to the severe RA. Excessive production of proinflammatory mediators activate macrophages which further secrete ROS in inflamed synovial fluid that leads to destruction of joints and cartilage (Direito et al. 2021; Kakkar et al. 2020; Seven et al. 2008). High production of oxidative stress causes mitochondrial dysfunctions that leads to alteration in apoptosis and autophagy balance (Frantz and Wipf 2010; Sena and Chandel 2012). Several studies also reported that IL-6 plays a significant role in worsening of authophagy as well as alter activity of IL-7 by mTOR, janus kinase and signal transducer and activator of transcription (JAK-STAT) and AMPK pathways that leads to permanent joints damage (An et al. 2018; Camporeale and Poli 2012; Harris 2011). In addition, several free radicals including superoxide (O_2), hydrogen peroxide (H_2O_2), hydroxyl radical (OH^-) and peroxynitrite ($ONOO^-$) are extremely reactive species that may lead to oxidative damage and tissue injury in joints of RA patients (Ananth et al. 2016). Significance factors such as environmental as well as genetic factors, are responsible for progression of RA, eventually leading to the barbarity (Bathon et al. 2000). A major risk factor among all the environmental factor is smoking and people are more prone to RA who smoke daily (Viatte, Plant, and Raychaudhuri 2013). Additionally, other environmental factors which contribute in the progression of RA are silica exposure, hormonal imbalance, exposure to stimuli such as bacteria, virus and stress, dietary factors and socioeconomic factors.

However, various recent medications and therapies including T-cell activation blockers (CTLA-Ig), rituximab (β-cell depletors), tocilizumab (IL-6 inhibitors) and TNF inhibitors have depicted remarkable effects as compared to conventional therapy like disease modifying anti-rheumatic drugs (DMARDS) or methotrexate treatment but still these therapies lack conclusive evidences related to treatment resistance (Tanaka, Ogata, and Narazaki 2013; Tanaka, Narazaki, and Kishimoto 2018). Besides the high efficacy of tocilizumab, there are also more possibility of failure of treatment and remission of RA disease (Kihara et al. 2017). Furthermore, RANKL antibody, JAK-STAT inhibitors or anti-CD20 antibody has developed as a new therapy for the amelioration of RA (Kim and Moudgil 2017). Despite the advancement in therapeutic strategies, it makes the treatment of rheumatoid arthritis very expensive and have still lower efficacy (Nandi, Kingsley, and Scott 2008; Roubille et al. 2015). Besides the favorable effects, conventional therapy also causes some serious side effects such as cardiovascular disease (myocardial infraction), renal infection, gastrointestinal infections (ulceration and bleeding) and hepatotoxicity (Roubille et al. 2015; Crofford 2013). Therefore, new approach is required for the management of immune dysfunction with less adverse effects.

Dietary polyphenols play a pivotal role in the management of human health (Wai Kan Yeung et al. 2018). Such natural polyphenols demonstrate anti-oxidant, anti-inflammatory and immunosuppressant activities that lead to the treatment of various inflammatory and autoimmune diseases including rheumatoid arthritis and inflammatory bowel disease (Direito et al. 2021). Over the past few years, polyphenols tend to reduce the pain and swelling as well as gained a significant attention in the area of research (Hughes,

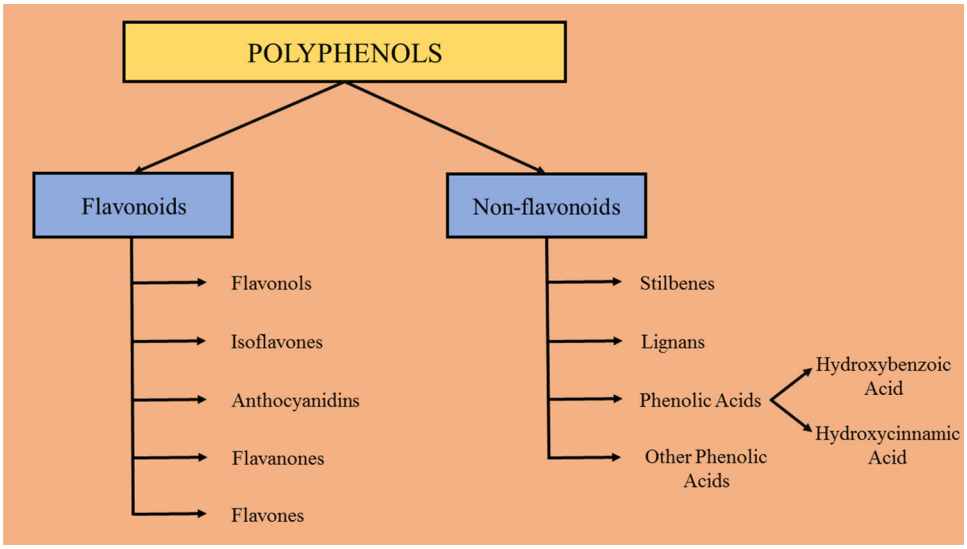


Figure 1. Classification of polyphenols.

Ketheesan, and Haleagrahara 2017). Polyphenols are secondary metabolites and are naturally administered with daily diet, till date, more than 8000 polyphenols compounds have been recognized (Magrone et al. 2019; Ganesan and Xu 2017). They are mostly present in tea, coffee, legumes, fruits and green vegetables (Ganesan and Xu 2017; Belwal et al. 2018). Polyphenols may be divided into five broad categories: phenolic acids, stilbenes, flavonoids, tannins and other phenolic compounds (Figure 1) (Petti and Scully 2009; Mateen et al. 2016). They have protective action against various pathogenic organisms in plants. These compounds showed anti-rheumatic property by inhibiting inflammatory cytokines and also possess anti-atherogenic, anti-osteoprotic and antioxidant properties. In addition, these agents also play favorable therapeutic effects by blocking ultraviolet radiations. Recently, various preclinical and clinical trials data have revealed that polyphenol rich diet have anticancer, antithrombotic, cardioprotective and antidiabetic activity (Pandey and Rizvi 2009). The favorable therapeutic activity of various polyphenolic compounds such as resveratrol (RSV) (Oliveira et al. 2017), epigallocatechin (EGCG) (Wu et al. 2012), capsaicin and curcumin (Dahan, Segal, and Shoenfeld 2017) in autoimmune disorders have been well studied. On the basis of anti-inflammatory and other therapeutic properties, the author give a vivid description and summarize the anti-rheumatoid activity of polyphenols (Figure 2).

It is a well-known that in autoimmune disorder, polyphenols exhibit a potent antioxidant activity which decrease the harmful consequences of reactive species generated by the over stimulation of the immune system. Additionally, polyphenolic compounds are the pharmacologically active components having immunomodulatory properties (Ding, Jiang, and Fang 2018). However, the assessment of the pharmacological efficacy is challenging due to variability in structural and bioavailability of these compounds. Furthermore, each polyphenolic compound targets a specific type of immune cell to regulate the immune system of subjects. The alteration of various signaling pathways by polyphenols cause modification in the expression of pro-inflammatory genes. The modification of cyclooxygenase (COX), phospholipase A2 (PLA2) further leads to regulate the differentiation and proliferation of specific immune cells. Moreover, their anti-inflammatory and antioxidant activity facilitate the modulation of entire inflammatory process (Malireddy et al. 2012; Santangelo et al. 2007; Khan et al. 2019). However, various conventional therapeutic medications have been marketed which can alter these signaling pathways but show severe side effects. Thus, in recent years, natural polyphenols have gained much attention as anti-inflammatory agents by targeting these pathways and less or no side effects (Khan et al. 2019).

Arachidonic acid pathway

Arachidonic acid, a polysaturated fatty acid, found in the phospholipid membrane by the influence of PLA2. Numerous enzymes such as lipoxygenase (LOX) and cyclooxygenase (COX) which target arachidonic acid and prompt the production of thromboxanes A2 and prostaglandin or leukotrienes and hydoxyeicosatetraenoic acid, respectively (Santangelo et al. 2007). The formation of these lipid mediators lead to inflammatory process and also these are the main target sites for the therapeutic agents to ameliorate the inflammation. Therefore, the direct inactivation of these pro-inflammatory enzymes is one of the most operative mechanism by which natural polyphenols regulate the inflammatory responses (Yoon and Baek 2005). It has been demonstrated that PLA2 was the first enzyme on which polyphenols including kaempferol, galangin and quercetin exhibited an inhibitory activity (Dreiseitel et al. 2009, Lättig et al. 2007). Moreover, p-coumaric and resveratrol bind directly with PLA2 residues and inhibiting the catalytic process (Shukla et al. 2015). A study revealed that honokiol and quercetin stimulated the SH-SY5Y neuroblastoma cells differentiation and blocked cystolic phosphorylation of PLA2

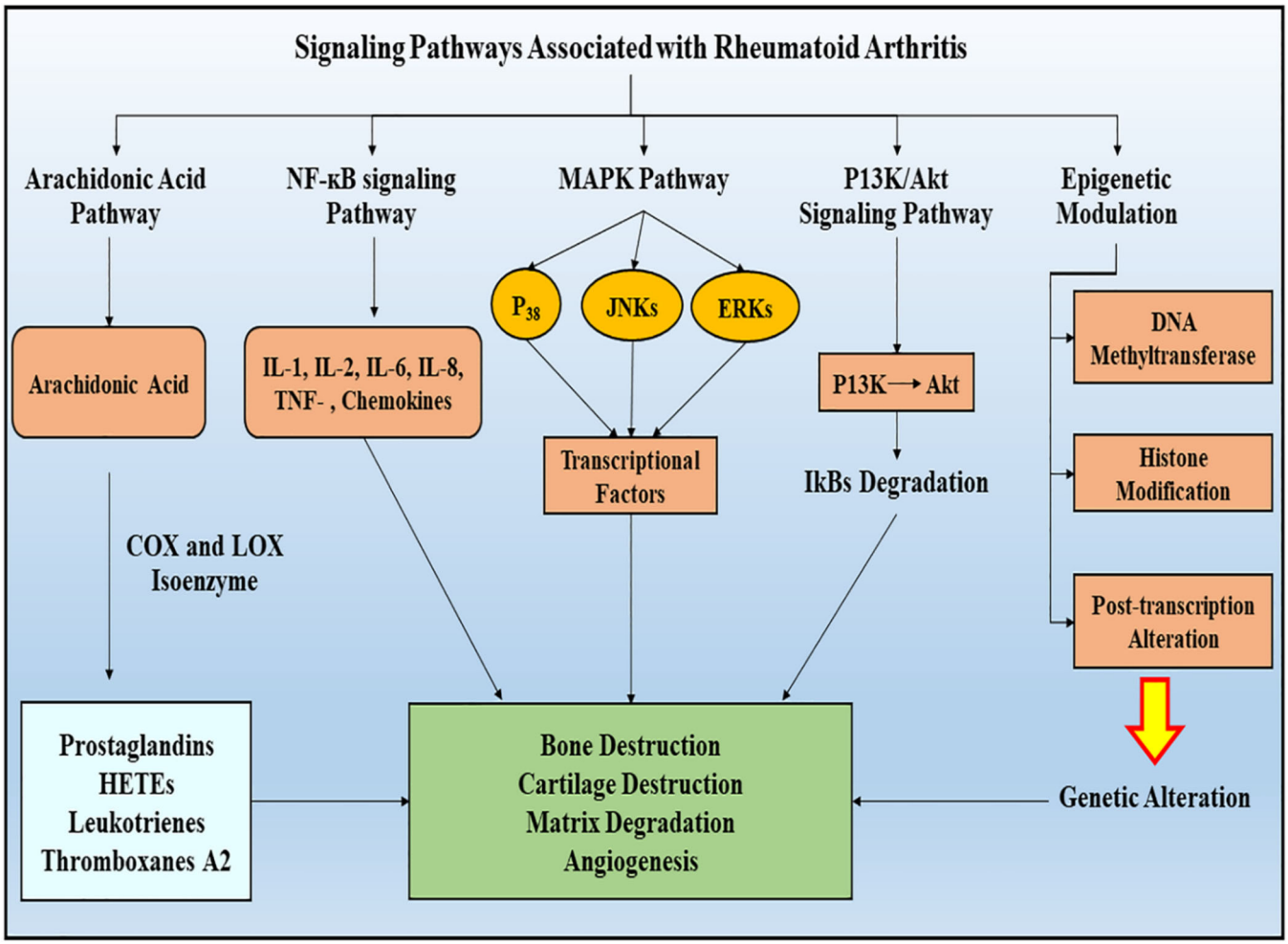


Figure 2. Signaling pathways associated with rheumatoid arthritis.

(Chuang et al. 2016). Evidences also suggested that flavonols are prominently LOX inhibitors while flavones are COX inhibitors (Kim et al. 2004).

NF-κB signaling pathway

NF-κB signaling pathway plays a pivotal role in the inflammatory process. It regulates and control the expression of various genes involved in the inflammatory process such as pro-inflammatory cytokines (IL-1, TNF-α, IL-6, IL-8 and IL-2), COX-2, chemokines (MCP-1 and MIP-1α and IL-18), vascular cell adhesion protein (VCAM)-1, intercellular adhesion molecules (ICAM)-1 and other growth factors (Liu et al. 2017; Nam 2006). Polyphenols have capability to alter multiple steps involved in the NF- κB signaling pathway. As per the antioxidant properties of polyphenols, they decrease the production of reactive species especially H_2O_2 and ROS subsequently, control the redox signaling pathway (Simon et al. 2018). Hence, it is supposed that these reactive species accelerate the stimulation of NF-κB pathway via redox process and act as a secondary messenger (Bowie and O'Neill 2000). Additionally, natural polyphenols firstly inhibit the phosphorylation, later, breakdown of inhibitory proteins (I_kB_S) by modifying the stimulation of I_kB_S kinase (IKK) and binding with the DNA (Yahfoufi et al. 2018). Polyphenol such as resveratrol, genistein, quercetin and EGCG have prominent capability to inhibit NF-κB pathway. Resveratrol inhibits the stimulation of NF- κB by inactivating the phosphorylation of I_kB_S and activation of IKK (Capiralla et al. 2012). A study reported that genistein inhibits the activation of NF-κB as a result, decrease the overproduction of IL-6 and TNF-α in macrophages 264.7 cells (Ji et al. 2012). This inhibitory mechanism was prominently associated with the blockage of I_kB_α degradation P65 translocation and IKK expressions in the nucleus (Li et al. 2014). Furthermore, EGCG also inhibited the NF-κB pathway by blocking P65 phosphorylation which is excited by IL-1β in human A549 respiratory endothelial cells (Wheeler et al. 2004).

Mitogen activated protein kinase pathway (MAPKs)

Mitogen, growth factor and stress play a pivotal role in the activation of MAPK pathway and management of genes associated with inflammatory response (Kim and Choi 2010). The prominent activity of polyphenols mainly depends upon the target cells on which they act. Numerous studies have showed an inhibitory activity of natural polyphenolic compounds on ERK1/2, JNK and p38/SARK pathways. This inhibitory activity suppressed the expression and

production of pro-inflammatory mediators including TNF-α and others. Quercetin has been reported inhibitory effects by altering the phosphorylation and stimulation of JNK in RAW 264.7 macrophage cells and preventing the binding of AP-1 with DNA. Furthermore, quercetin also inhibited the activation of P38 and ERK1/2 (Wadsworth, McDonald, and Koop 2001). EGCG has also exhibited anti-inflammatory activity in LPS activated macrophages by suppressing the activation and phosphorylation of MAPK pathway (Ahn et al. 2004). The treatment of resveratrol with IL-1β stimulated rat RSC-364 synovial cells, inhibited the JNK and P38 signaling pathway (Lou et al. 2018; Yang et al. 2018). Other polyphenols including hesperidin, chrysin, luteolin, kaempferol and naringin have also been demonstrated anti-inflammatory effects by altering the MAPK signaling pathway (Kim, Kim, and Kim 2011).

Phosphatidylinositol-3-kinase/protein kinase B (PI3K/akt) signaling pathway

In autoimmune disorders especially rheumatoid arthritis, PI3K/Akt signaling pathway plays a crucial role by inducing the breakdown of I_kB and the stimulation of NF-κB (Sun et al. 2010). Numerous natural polyphenols exhibit their anti-inflammatory activity through inhibitory PI3k/Akt pathway. The treatment of resveratrol decreased the expression of IL-17, a pro-inflammatory cytokines, in cardiac fibroblast by inhibiting PI3k/Akt pathway (Venkatachalam et al. 2008). Quercetin reduce the Akt phosphorylation in JB6 mouse model by direct inhibiting PI3K (Busch et al. 2012). An anti-inflammatory effects of isorhapontigenin was also observed by suppressing the NF-κB activation, production of chemokines CXCL8 and IL-6 and inhibiting PI3k/Akt pathway (Yeo et al. 2017).

Epigenetic modulation

Alteration in epigenetic pattern including histone modification, DNA methylation, posttranscription alteration by microRNAs and modification of immune responses play a significant role in the pathophysiology of RA (Rahman and Chung 2010). Numerous studies have revealed that polyphenols have ability to regulate these epigenetic mechanisms through gene activation and modification in the DNA sequences (Ayissi, Ebrahimi, and Schluesenner 2014). Among several polyphenolic compounds, resveratrol have more potential to activate SIRT1, which leads to the inhibition of NF-κB and associated genes including iNOS and COX-2 (He et al. 2017; Liu et al. 2016). Other polyphenols such as fisetin, curcumin, quercetin and myricetin have also ability to activate SIRT1 and downregulated the occurrence of RA (Zhao et al. 2017; Zheng et al. 2017; Boyanapalli and Kong 2015; Hong et al. 2012). Furthermore, resveratrol have also ability to act on DNA methyltransferases subsequently, enhances their activity as well as expressions. MicroRNAs such as miR-181b and miR-21 are non-coding regulatory RNAs, having ability to regulate degradation and translocation of messenger RNAs which further associated with occurrence of RA. Various study have reported anti-inflammatory effects of polyphenolic compounds by modulating microRNAs (Maugeri et al. 2018). A study reported that curcumin upregulated the expression of miR-181b consequently, decreased the levels of pro-inflammatory chemokines such as CXCL1 and CXCL2 (Kronski et al. 2014). Another study showed that resveratrol reduced expression of miR-21 resulting in reduction of inflammatory responses (Li et al. 2013).

Therapeutic significance of polyphenols

Natural polyphenols are most widely used phytochemicals in human diet for their antioxidant activity (Grootaert et al. 2015). These component have multifactorial activity such as antimicrobial (protect against viruses, fungi and bacteria) (Steinmann et al. 2013), antiasthma (Joskova et al. 2013), anxiolytic, antidepressant (Bouayed 2010), cardioprotective (Mokni et al. 2007), antidiabetic (Umeno et al. 2016), anticarcinogenic (Du et al. 2012) and neuroprotective (Ullah and Khan 2018)) actions. The antioxidant property of these natural polyphenols helps in the management and prophylaxis of age-related complications (Zhao et al. 2016; Figueira et al. 2017). Polyphenols exhibit anti-modulatory activity, thus have potent therapeutic actions against the autoimmune disorders (Ding, Jiang, and Fang 2018). At present, in the treatment of autoimmune disease (rheumatoid arthritis), a combination therapy is used. Such combinations are DMARDS with other individual drugs as the synergic action in rheumatoid arthritis but yet did not give any satisfied results. Thus, due to their potent anti-inflammatory actions, researchers showed a great interest in polyphenols for the management of rheumatoid arthritis (Betancourt et al. 2018; Sung et al. 2019).

Phenolic acids

Hydroxybenzoic acid and hydroxycinnamic acid are the main components of phenolic acids. Phenolic acids are present in all natural plants but the high content of phenolic acids are found in sour and citrus fruits. Additionally, in regular diet, phenolic acids contain about one third of the polyphenolic compounds. Gallic acid, cinnamic acid, ferulic acid, isoferulic acid and caffeic acid are few typical examples of phenolic acids (Doss et al. 2018; Sung et al. 2019). These compounds have tendency to donate an electron from aromatic phenolic rings and migrate a hydrogen atom to convert into free radicals. Thus these agents act as reducing agents and free radical scavengers (Sevgi, Tepe, and Sarikurkcu 2015). In addition, mainly hydroxybenzoic acid has ability to stimulate various endogenous antioxidant pathways to enhance the levels of antioxidant enzymes (Juurlink et al. 2014). Generally, the content of hydroxybenzoic acid in edible plants is low, except raspberries, blackberries, strawberries, onion and black radish (Naczk and Shahidi 2006).

Doss et al. examined the action of ferulic acid on bone erosion and osteoclast differentiation by using the isolated

monocyte and macrophage cells of wistar rats. The cells were pre-exposed with ferulic acid for 24 hours. SEM and TRAP analysis were used for evaluation of osteoclast formation and differentiation while pit formation assay was performed for analysis of bone erosion. Results revealed that treatment of ferulic acid, present in grain, nuts, fruits and vegetables, suppressed the NF-kB, tartrate resistant acid phosphatase (TRAP), cathepsin, matrix metalloproteinase (MMP)-9, nuclear factor of activated T-cells C-1 (TFATC1) activities. In addition, a remarkable reduction in bone resorption was also observed (Doss et al. 2018). Poscavo et al. performed a comparative study to evaluate the immunomodulatory activity of polyphenol N-feruloylserotonin (Nf-5HT) with methotrexate (MTX) and standard therapy of RA. The study included two type of animals: arthritic rats as treatment group and healthy rats as control group. Arthritic rats were treated with either Nf-5HT or MTX for 28 days. Treatment of both Nf-5HT and MTX reduced the levels of C-reactive protein (CRP), inducible nitric oxide synthase (iNOS), TNF-α and also decreased the activity of 12/15 LOX in the liver. Moreover, in Nf-5HT treated group, the attenuation in IL-1β levels in plasma and IL-1β expression in spleen and liver was also observed which was not seen in methotrexate treated group (Pašková et al. 2016).

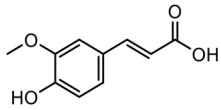
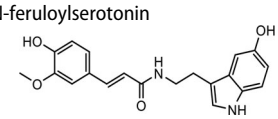
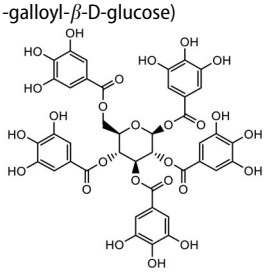
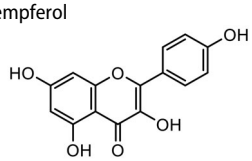
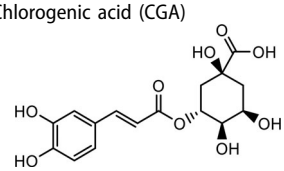
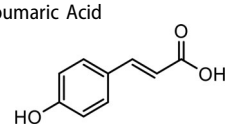
Lee et al. demonstrated the efficacy of gallotannins polyphenols (*euphorbia* species) on pro-inflammatory cytokines and TF-$\kappa\beta$ by using mast cell line. Mast cells prompt the production and synthesis of proinflammatory mediators like IL-1β, IL-6 and TNF-α. A dose dependent manner was observed by the gallotannins in reduction of proinflammatory cytokines release and gene expression. In addition, the treatment of gallotannins significantly reduced the levels of TNF-α (Lee et al. 2007). Kwak and colleagues evaluated the efficacy of *Gardenia jasminoides* derived chlorogenic acid in RANK induced osteoclast. In bone marrow macrophages, chlorogenic acid treatment inhibited the osteoclast differentiation without any experience of cytotoxicity. It also reduced the phosphorylation of AKT and also conquered the expression of nuclear factor activated T-cells. Moreover, in vivo, the treatment of chlorogenic acid (10,25,50 µg/mm) with bone marrow macrophage for 4 days, also alleviated the bone erosion induced by lipopolysaccharide (Kwak et al. 2013). In-vivo study conducted by the Pragasom et al. examined the anti-inflammatory as well as immunomodulatory activity of p-coumaric acid by using same dose of treatment (100 mg/kg). Serum immunoglobulin levels, macrophage phagocytic index and cell mediated immune response were analyzed to examine the immunomodulatory actions while TNF-α expressions were analyzed to investigate anti-inflammatory action. The treatment of p-cumaric acid reduced the elevated macrophage phagocytic index and cell mediated immune response by alleviating immunoglobulin, thus showed immunosuppressive activity. Additionally, the intervention of p-cumaric acid in adjuvant-induced arthritic rats also exhibited anti-inflammatory activity by reducing the expression of TNF-α (Pragasam, Venkatesan, and Rasool 2013). Another study by Neog et al. showed the efficacy of p-cumaric acid by using adjuvant induced arthritic rat model. The treatment of p-cumaric acid for 16 days, significantly reduced TNF-α activation and also showed anti-RA activity by attenuating chemokines, cytokines, osteoclastogenic factors, MAPK and transcriptive factors. The major alteration in chemokines and cytokines including IL-6, IL-1β, monocyte chemoattractant protein (MCP)-1, pro-inflammatory cytokines including IL-16, IL-6, IL-17, osteoclast factors including RANKL, the transcriptive factors including c-Fos, NF-κB-p65, NF-ATc-1 and P-NF-κB-p65 was observed (Neog et al. 2017) (Table 1).

Stilbenes

Stilbenes are the non-flavonoid polyphenolic compounds which are characterized by occurrence of 1,2-diphenylethylene nucleus. On the basis of nucleus, stilbenes may be divided into two type: Z-stilbenes (cis-isomers) and E-stilbenes (trans-isomers) (Sirerol et al. 2016). These compounds are found in large number of natural plants, having defensive actions. No doubt, more than 400 stilbene compounds have been identified but the occurrence of these compounds is limited as they present in heterogeneous plants. Berries, red wine, grapes and peanuts are the some examples of which contain these compounds (El Khawand et al. 2018). Wine is a major source of stilbenes in daily diet as it contains 98.4%, grapes juice and grape berries contain 1.6% while other contain less than 0.01% (Zamora-Ros et al. 2008). Stilbenes mainly have antioxidant, anti-inflammatory and cell death activation properties. Resveratrol is a well-known component of stilbenes which is prominently present in outer layer (skin) of grapes. At present, 20 metabolites of resveratrol have been recognized having specific activity. Although, the bioavailability of resveratrol is limited as it depends on metabolism. Numerous studies have demonstrated the potential effects of resveratrol. Resveratrol have tendency to suppress the arthritis induced by inflammatory factors (El Khawand et al. 2018; Wang et al. 2019).

Zang et al. conducted a study on fibroblast like synoviocytes (FLS) of adjuvant-arthritic rats, to evaluate the anti-rheumatoid arthritis action of resveratrol obtained from red grapes. Rats were administered with 5, 15, 45 mg/kg dose of resveratrol for 12 days. Results showed a significant reduction in swelling and malondialdehyde levels. In addition, resveratrol treatment also inhibited LC3A/B, Beclin1, mtROS and manganese dependent superoxide dismutase (MnSOD) (Zhang et al. 2016). In another study, 50 µg of resveratrol on FLS in human for 24 hours showed anti-RA activity via suppressing prostaglandin E2, AKT, nicotinamide adenine dinucleotide (NADPH), COX-2, ROS, NF-KB, ERK1/2 and P38 MADK (Tsai et al. 2017). Tian et al. conducted a study on human synovial membrane to investigate the anti-rheumatoid activity of resveratrol by using a dose 6.25, 12.5, 25, 50 µM. Resveratrol treatment suppressed IL-1β, p-AKT, MMP-3 and PI3K-AKT (Tian et al. 2013). Khojah et al. conducted a randomized clinical trial to investigate the anti-rheumatic activity of resveratrol in RA patients. The study included 100 subjects with RA (65 female and 32 male) and divided into 2 groups. Resveratrol treated group received 1 g

Table 1. Suppression of rheumatoid arthritis by phenolic acids.

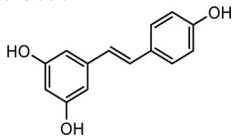
Source	Compound	Dose/Duration	Animal model/ cell Line	Mechanism	References
Grain(Wheat, oats and rice), nuts, fruits and vegetables	Ferulic acid 	25, 50, 100 μM/24 h	Monocyte/ macrophage cells/Rat	↓ NF-κB, c-Fos, NFATc1, MMP-9, TRAP, Cathepsin	Doss et al. (2018)
Leuzea cartamoides	N-feruloylserotonin 	3 mg/kg/28 days	AA	↓ INOS, CRP, LOX, IL-1β, TNF-α	Pašková et al. (2016)
Euphorbia	Gallotannins (1,2,3,4,6-penta-O -galloyl-β-D-glucose) 	10 mg/ml/30 min	HMC-1/human	↓ NF-κB, TNF-α, IL-6, IL-1β	Lee et al. (2007)
Gallic acid	Kaempferol 	100 μM/2 days	RASFs/human	↓ COX, IL-1β, PGE2, MMPs	Yoon et al. (2013)
Gardenia jasminoids	Chlorogenic acid (CGA) 	10,25,50 μg/mM/4 days	Osteoclast/ BMMs	↓ P38, ERK, Akt, NF-κB	Kwak et al. (2013)
Gnetm cleistostachyum	p-Coumaric Acid 	100 mg/kg/8 days	AIA rat	↓ CIC, TNF-α ↑ IgG	Pragasam, Venkatesan, and Rasool (2013)
Gnetm cleistostachyum	p-Coumaric Acid	100 mg/kg/16 days	AIA rat	↑ TRAP, IL-6, RANKL, IL-17, NF-κB-p65, IL-1β, MCP-1, TNF-α, cFOS, COX-2, iNOS, NFATc-1, p-NF-κB-p65, JNK, ERK1/2, p-JNK ↑ OPG	Neog et al. (2017)

NF-κB: nuclear factor κ light chain enhancer of activated B cells; IgG: immunoglobulin G; TNF-α: tumor necrosis factor-α; AA: adjuvant arthritis, RASFs: rheumatoid arthritis synovial fibroblasts; HMC: human mast cell line; IL-1β: interleukin-1β; TRAP: tartrate-resistant acid phosphatase; NFATc1: nuclear factor of activated T cells c1; BMMs: bone marrow-derived macrophages; AIA: adjuvant induced arthritis; COX: cyclooxygenase; RANKL: receptor activator of nuclear factor kappa-B ligand; MCP-1: monocyte chemoattractant protein-1; CIC: circulating immune complexes; LOX-12/15: lipoxygenase; MMP-9: matrix metalloproteinases-9; iNOS: inducible nitric oxide synthase; OPG: osteoprotegerin; JNK-c: Jun N-terminal kinases; BMMs: bone marrow-derived macrophages; PGE2: prostaglandin E2; CRP: C-reactive protein.

RSV capsule daily with standard therapy for three months and control group administered only regular treatment. Clinical biomarkers analyzed after the treatment period. Results showed that RSV treatment significantly reduced the levels of various inflammatory biomarkers including SJC-28, erythrocyte sedimentation rate (ESR), TJL-28, uncarboxylated osteocalcin, CRP, TNF-α, MMP-3, IL-6 and immunosuppressant activity (Khojah et al. 2018).

In vitro study performed by Tang showed the anti-apoptotic activity of resveratrol. TUNEL, flow cytometry, colourmetric and western blot assay were performed to assess the apoptosis, caspase3 activity and pro-caspase3 cleavage. Study

Table 2. Suppression of rheumatoid arthritis by stilbenes.

Source	Compound	Dose/Duration	Animal model/ cell Line	Mechanism	References
Polygonum cuspidatum	Resveratrol 	200/400 mg/kg, daily	BIIC & IL-1β induced rats	↓ ROS, MAPK, angiogenesis, cell proliferation	Yang et al. (2018)
Red grapes	Resveratrol	5/15/45 mg/kg/12 days	AA/FLSs	↓ Beclin1, MnSOD, LC3A/B ↑ MtROS	Zhang et al. (2016)
Red grapes	Resveratrol	50 μg/24 h	Human/FLSs	↓ PGE2, MAPK, p38, ERK1/2, COX-2, NF-κB, NADPH oxidase	Tsai et al. (2017)
Red grapes	Resveratrol	6.25, 12.5, 25, 50 μM/1 h	Human/FLSs	↓ P-Akt, MMP-3, IL-1β, PI3K-Akt	Tian et al. (2013)
Red grapes	Resveratrol	1000 mg/day/3 months	Randomized control clinical trial	↓ MMP-3, IL-6, TNF-α, RF	Khojah et al. (2018)
Red grapes	Resveratrol	30 μM, 50 μM/ 3 days 20 mg/kg/10 days 40 μM/72 h	Th17 cell/CIA CIA DLN cell/CIA	↓ IL-17, Th-17 ↓ IgG1, IgG2a ↓ IFN-γ, IL-17	Xuzhu et al. (2012)
Red grapes	Resveratrol	10 mg/kg/day/7 days	CFA induced rat	↓ MMP-3, RF, IgG, TNF-α, ANA, MDA, MPO, COMP ↑ GSH, IL-10	Wahba, Messiha, and Abo-Saif (2016)

CIA: collagen-induced arthritis; MnSOD: manganese-dependent superoxide dismutase; NF-κB: nuclear factor κ light chain enhancer of activated B cells; COX: cyclooxygenase; TNF-α: tumor necrosis factor-α; IFN: interferon; NADPH: nicotinamide adenine dinucleotide phosphate; MDA: malondialdehyde; PI3K: phosphoinositide 3-kinases; MtRO: mitochondrial ROS; LC3: microtubule-associatedprotein 1a/1b-light chain 3; ROS: reactive oxygen species; MPO: myeloperoxidase; COMP: cartilage oligomeric matrix protein; PGE2: prostaglandin E2; DL: draininglymph node; RF: rheumatoid factor; GSH: glutathione; ROS: reactive oxygen species; FLSs: fibroblast-like synoviocytes; MAPK: mitogen-activated protein kinase; ANA: antinuclear antibodies; CFA: cetylated fatty acids; IL-1β: interleukin-1β.

revealed that the treatment of resveratrol inhibit RA-FLS proliferation via activation of caspase3 expressions (Tang et al. 2006). Xuzhu et al. showed the anti-inflammatory activity of resveratrol by using collagen-induced arthritis mice model. RSV treatment (20 mg/kg) reduced the rheumatic symptoms by suppressing IgG1 and IgG2a. In addition, the treatment of resveratrol with Th-17 cells and draining lymph node cells also reduced TNF-α and IL-17. Furthermore, by using same cell line, resveratrol treatment suppressed Th-17 and IL-17. RSV was administered in FLS in arthritic animal revealed a reduction in LC3A/B, Beclin1 and MnSOD and increment in mitochondrial (Mt) ROS (Xuzhu et al. 2012; Wahba, Messiha, and Abo-Saif 2016). Yang and coworkers examined the effects of resveratrol in bovine type II collagen (BIIC) arthritis rat model and in-vitro RA model (IL-1β stimulated rat synovial cells). Study revealed that the treatment of resveratrol with a dose of 200 and 400 mg reduced the production of ROS, MAPK pathway, cell proliferation, inflammatory mediators and also angiogenesis induced by HIF-1α (Yang et al. 2018) (Table 2).

Flavonoids

Recently various dietary components found in fruits and vegetables have been identified and investigated for their favorable therapeutic effects. Most of them are flavonoids and non-flavonoids (de Villiers, Venter, and Pasch 2016). Although, all flavonoids have an identical structure with 2 phenyl rings which are connected with three carbon atoms forming a specific type of oxygenated heterocycle (Jackson et al. 2006; Manach et al. 2004). Flavonoids are the most common polyphenolic compounds present in wide variety of fruits, nuts, beverages and vegetables. These compounds are characterized with the presence of flavan nucleus. Recent data reported that more than 8000 flavonoid compounds have been recognized and most of them act as coloring agents for leaves, flowers and fruits (Castro-Acosta et al. 2016; Nijhawan and Behl 2020). Flavonoids can be classified into 6 categories: anthrocyanidins, flavones, flavanones, flavonols, isflavonols and flavan-3-ols. These compounds are considered as protective agents against various cardiovascular and cancer disease as they possess anti-inflammatory, antithrombotic and antioxidant activity. In addition, due to their low toxicity, these compounds can be safely administer in daily diet with significant amount (de Villiers, Venter, and Pasch 2016; Jackson et al. 2006). Furthermore, flavonoids also exhibited an anti-inflammatory actions by decreasing the formation of proinflammatory cytokines, eicosanoids, NF-κB, activating protein-1 signaling and Nitric oxide (Li et al. 2014; Serafini, Peluso, and Raguzzini 2010).

Tea, epigallocatechin-3-gallate, quercetin are the most common flavonoids. Citrus flavonoids have lipid modifying property thus, can be used in metabolic diseases (Kim, Vance, and Chun 2016). Hesperidin (HSP) is a prominent bioactive compound present in citrus fruit and have ability to suppress collagen induced arthritis (CIA). Kometani et al. investigated the anti-rheumatic effects of α-glycosylhesperidin (HSP-G), derivative of hesperidin in both rats and human. The study revealed that oral intervention of HSP-G with a dose of 3 mg/0.3 ml thrice in a week for 31 days, can ameliorate CIA. Additionally, HSP-G treatment reduced the production of TNF-α in mice model. Furthermore, in human study, Kometani et al. reported that the treatment of HSG-P along with standard therapy have potential effects in improvement of rheumatoid arthritis. Consequently, the standard of living can be improvised by HSP-G.

Haleagrahara et al. conducted a study to examine the anti-inflammatory and immunosuppressive activity of quercetin for the management of arthritis by using CIA rat's model. The animals were randomly assigned into 5 groups: 1st group-untreated (no arthritis), 2nd group-control group (with arthritis), 3rd group-arthritis and methotrexate, 4th group-arthritis and quercetin, 5th group-arthritis and methotrexate and quercetin. The therapeutic efficacy of quercetin was analyzed by assessing edema, weight, production of cytokines and joint destruction. Study revealed that the co-administration of methotrexate and quercetin did not exhibit much protective activity than the single agent administration. As a result, the ingestion of quercetin as monotherapeutic agent showed higher protection against joint inflammation. Additionally, the use of quercetin also suppressed the levels of IL-17, TNF-α, MCP-1 and IL-1β and showed anti-arthritic activity (Haleagrahara et al. 2017). Haleagrahara and coworkers conducted a study to evaluate the ant-inflammatory effects of quercetin in combination with methotrexate in CIA rat model. The rats were randomly allocated into 5 groups: 1st group-control group, 2nd group-arthritis group, 3rd group-methotrexate treated group, 4th group-quercetin treated group, 5th group- quercetin and methotrexate treated group. PCR ELISA assay was performed to analyze the activity of quercetin on inflammatory mediators. After the treatment of quercetin, a significant reduction in the expression of inflammatory mediators including MMP-3, MMP-9, TNF-α, IL-6 and IL-1β was observed (Haleagrahara et al. 2018).

Furthermore, Javadi et al. conducted a randomized, double blinded clinical trial on women having RA to examine the effects of quercetin on inflammation, disease severity and clinical symptoms of RA. Subjects were divided into two groups: 1st group-quercetin treated group and 2nd group-control group. Results revealed that administration of quercetin with a dose of 500 mg/day for 8 weeks remarkably decreased morning stiffness, morning pain and TNF-α levels compared to placebo treated group (Javadi et al. 2017). In another randomized, double blinded clinical trial treatment of quercetin with a dose of 500 mg/day for 8 weeks did not show any significant improvement in oxidative stress biomarkers in blood such as MDA, oxidized low density lipoprotein and high sensitivity C-reactive protein (hs-CRP) (Javadi et al. 2014).

He and coworkers showed the anti-oxidant and anti-inflammatory actions of anthocyanin by using adjuvant-induced arthritis (AIA) model. Study demonstrated that the ingestion of anthocyanin (40, 20, 10 mg/kg) for 14 days, reduced the levels of PGE2, TNF-α, superoxide dismutase and malondialdehyde (He et al. 2006). Kim et al. also investigated the antioxidant and anti-inflammatory effects of cocoa polyphenols. Cocoa polyphenols comprises catechin, epicatechin, procyanidine and flavonol glycosides were treated to the JB6 P + mouse epidermal cell with dose of 20 and 10 μML for 1 hour, decreased the upregualtion of NF-κB, vascular endothelial growth factor (VEGF) and AP-1 and enhanced the production of p-p70S6K, P-Akt, p-c-Jun N-terminal kinases (ERK), p-mitogen activated protein kinase kinase-4, P-extracellular signal regulated kinases (ERK), p-PI3K and p-p90KDa ribosomal S6 kinase (Kim et al. 2010). Epigallocatechin-3-gallate (EGCG) extracted from *camellia sinensis* exhibited anti-rheumatic action by reducing the levels of RANTES, epithelial neutrophil-activating peptide (ENA)-78, MMP-2 induced by IL-1 & chimokines and growth regulating oncogene (GRO)-α, when human rheumatoid arthritis synovial fibroblast (RASF) were treated at a dose of 50, 40, 30, 20, 10 μM for 12 hours (Ahmed, Pakozdi, and Koch 2006). EGCG also reported anti-rheumatic effects in RASFs by suppressing the production of MMP-1, MAPK, ERK1/2, p-p-38, p-JNK, AP-1 and MAPK when treated with a dose of 500, 250, 125 nM for 24 hours (Yun et al. 2008).

A study analyzed the efficacy of EGCG on osteoclast differentiation and T-cells differentiation in arthritis model. After the intervention of EGCG with a dose of 50, 40, 30, 20 mg/kg for three weeks, blocked the release of IgG2a, IL-6, IL-1β, nitrotyrosine, cFos, VEGF, IL-17, TNF-α, NFATc1, MMP9, p-STAT3 727, cathepsin K (CTSK), chemokine (C-C motif) ligand 6 (CCL6), IL-21, p-ERK, p-STAT3705, aryl hydrocarbon receptor (AHR), calcitonin receptor and tartrate resistant acid phosphate (TRAP) whereas stimulate IL-10, Foxp3, suppressor of cytokine signaling 3 (SOCS3) and TGF-β (Lee et al. 2007). Min et al. examined the immunomodulatory actions of EGCG in CIA rat model. The rats were administered with EGCG (10 mg/kg, treatment group) or phosphate buffer saline (PBS, control group) for 3 weeks. Results showed that EGCG treated group reduced the clinical symptoms of arthritis in rats. Additionally, administration of EGCG also suppressed TNF-α, IFN-γ and Il-6 while activated anti C II specific IgG1 antibodies as compared to PBS treated group and also elevated the levels of erythroid 2 like 2, hemeoxygenase (HO-1) and nuclear factor (Min et al. 2015). Recent studies reported that polymorphonuclear granulocytes and internal immune system also play a crucial role in early and destructive phase of RA. Leichsenring and colleagues demonstrated the anti-rheumatic effects of EGCG by using pristine induced arthritis (PIA) rat model. Study revealed that the intervention of EGCG at a dosage of 10 mg/kg for 5 days inhibited the myeloperoxidase actions thus promote the use of EGCG polyphenolic compound in arthritis (Leichsenring et al. 2016). Morinobu et al. evaluated the therapeutic effects of EGCG on osteoclasts differentiation. Both mice and human osteoclast (separated from human peripheral monocyte) were treated with EGCG (20 mg/kg) for 15 days. After 15 days administration, EGCG down regulated the CTR, Cathepsin K, carbonic anhydrase II, NF-ATc1, β-3 integrin and α-v integrin (Morinobu et al. 2008). MMPs play an imperative role in the osteoporosis and rheumatoid arthritis. Administration of EGCG at a dose of 10 and 100 μM lowered the formation of multinucleated osteoclast MMP-2 and MMP-9 thus, exhibited antirheumatoid effects (Oka et al. 2011). Many studies have been reported that the up-regulation of production of IL-17 and Th-17 response play a key role in progression of RA. Lee et al. examined the antirheumatoid activity of EGCG on osteoclastogenesis and T-cell differentiation by using TNF-

γKO and CIA rat models. Study revealed that the administration of EGCG with a dose of 20 or 50 mg/kg, three times per week, significantly suppressed the arthritis score as compared to control group. In addition, EGCG treated group also showed less occurrence of cartilage destruction, inflammation and CII antigen specific IgG2a levels than control group while anti-inflammatory IgG1s levels were augmented. Moreover, the treatment of EGCG with 50 mg/kg also reduced the expressions and production of IL-6, VEGF, IL-17, IL-1β, TNF-α, nitrotyrosine, iNOS and P-STAT3 705/727. In interferon-γ knockout rat, the administration of EGCG suppressed the levels of Th17 as well as osteoclastogenesis and ameliorated the symptoms of rheumatoid arthritis (Lee et al. 2009). Yang et al. conducted a study to evaluate the effect of EGCG on IL-1 receptor antagonist knockout (IL-1RaKO) autoimmune arthritis model. In this study, EGCG was injected in IL-1RaKO model with a dose of 40 mg/kg, 3 times/week. After the intervention, blood samples were analyzed. Results revealed that EGCG treatment reduced the arthritis index and ameliorated the joint damage in animal model. Additionally, EGCG also suppressed the production and expression of oxidative stress, pro-inflammatory cytokines, p-STAT3 (S723), p-STAT3 (S705), HIF-1α and mTOR in animal model. A dose dependent manner was observed in the reduction in formation of osteoclast, T-cell proliferation and serum level of both IgG2a as well as CII IgG2a (Yang et al. 2014).

Fisetin, a flavonoid, extracted from *Rhus verniciflua* Stokes, exhibited anti-rheumatic activity. Lee et al. reported that fistein inhibited the expressions of IL-6, TNF-α, MCP-1, IL-8, FLS proliferation and VEGF when it was treated with RAFLS with dose of 0.1, 1 or 10 μg/ml for 72 hours (Lee et al. 2016). Flavonol-rich residual layer of hexane fraction extracted from *Rhus verniciflua* Stokes also repressed the expressions of IL-8, TNF-α, FLS proliferation, MCP-1, IL-6 and IL-1β. Moreover, reduced the phosphorylation of p-JNK and p-ERK while stimulate phosphorylation of P38MAPK (Lee et al. 2016). Rathi et al. evaluated the anti-rheumatoid arthritis effects of gallic acid, derived from bark of *cinnamomum zeylanicum*, by using various animal models of arthritis. Study revealed that the treatment of gallic acid (40 mg/100 μL) with concanavalin-stimulated lymphocytes suppressed the expressions of cytokines including INF-γ, IL-2 and IL-4. Moreover, the treatment of gallic acid (200 mg/kg) with AIA rats for 10 days repressed the expressions of TNF-α without causing any adverse effects. Thus, both studies favor anti-rheumatic activity of gallic acid (Rathi et al. 2013). Genistein is a polyphenolic compounds found in soybean has reported a potent anti-inflammatory actions. A study conducted by Wang et al. showed anti-RA effect of genistein by using CIA rat models. Administration of genistein, downregulated the expressions of t-bet, TNF-γ and Th1/Th2 while upregulated IL-4 and GATA-3 expressions at a dose of 1 mg/kg for 42 days (Wang et al. 2008). In another study, genistein exhibited identical anti-RA actions in RAFLS by inhibiting MMP-9 and FLS proliferation with a dose of 10 μg/ml for 24 hours (Zhang et al. 2012). Li et al. also reported the anti-rheumatic activity of genistein in NH7A cells by blocking the release of IL-6, IL-1β and IL-8. In addition, resveratrol inhibits the NF-κB/Akt/ROS pathway and activate adenosine monophosphate activated protein kinase signaling pathways (Li et al. 2014). Umar et al. reported the anti-inflammatory effects of hesperidin by CIA rat models. After 24 days intervention of hesperidin (160 mg/kg), suppression in the levels of nitric oxide, lipid peroxidation and articular elastage was observed. Further, hesperidin enhanced SOD, catalase and glutathione (GSH) expression (Umar et al. 2013). Kaempferol is a potent flovonol obtained a wide variety of natural plants including beans, kale, broccoli, spinash, grapes fruits and teas. A study analyzed the potential anti-RA actions of kaempferol on synovial tissue having knee arthroplasty. The treatment of kaempferol with dose of 200, 100, 50, 10 μM for 2 days on synovial tissue, ameliorated NF-κB, MAPK and RASFs while the treatment with 100 μM for 48 days, suppressed the expressions of NF-κB, MAPK, COX-2, PGE2, MMP-3 and MMP-1. Thus, both results favors the anti-rheumatic effects of kaempferol in synovial tissues (Yoon et al. 2013). Malvidin (malvidin-3-O-β- glucoside) is a potent anthocyanidins which is responsible for the coloring of red fruits and red wine. Decendit and coworkers reported the anti-RA effects of malvidin, extracted from red grapes skin powder, by ameliorated clinical symptoms of rheumatoid arthritis. When 1, 10, 100 μM dose of malvidin were treated with human peripheral blood monocyte derived macrophages for 1 days, suppression in macrophage inflammatory protein 1 a (MIP1a), IL-1, IL-8, IL-6, NO, NOx, and TNF-α was observed. In addition, the treatment of malvidin in peritoneal macrophages of rats with same conditions, repressed the actions of IL-18, TNF-α and IL-1β (Decendit et al. 2013). Mangiferin (1,3,6,7-tetrahydroxy xanthone-C2-β-D-glucoside) is an essential bioactive compound of *Phaleria cumingii* (Thymelaeaceae family), exhibited anti-rheumatic actions in CIA rat models. The administration of mangiferin for both 27 and 14 days with a dose of 100 and 400 mg/kg, suppressed the expressions of IL-6, RANKL, TNF-κB, ERK1/2 and TNF-α (Tsubaki et al. 2015). Sultana et al. examined the anti-rheumatoid effects of morin, a dietary polyphenol, present in numerous fruits and vegetables, in spleen and synovial macrophage by using AIA rats model. The administration of ML-morin at a dose of 10 mg/kg for three days significantly ameliorated the formation of proinflammatory cytokines (IL-1β, IL-6, IL-17, and TNF-α), an inflammatory enzyme (iNOS), transcriptive factor (NF-κB-p-65), angiogenic factors (VEGF), STAT-3, MCP-1 and RANKL (Sultana, Neog, and Rasool 2017). Kumar and colleagues conducted a study to evaluate the efficacy of mangiferin extracted from *swertia chirayita* stem on the levels of proinflammatory and anti-inflammatory mediators in joint synovium. After 12 days administration of mangiferin, it reduced the expressions of IL-1, TNF-α, TNF-γ, and elevated the levels of IL-10 in a dose dependent manner (Kumar et al. 2004). Another study also reported the anti-rheumatic activity of mangiferin by suppressing the synthesis of PG E2 and expressions of COX-2. In addition, mangiferin also significantly ameliorated the production of 8-iso-prostaglandin

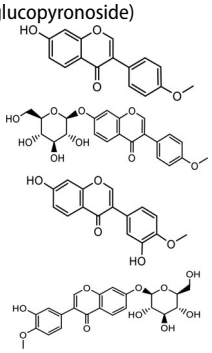
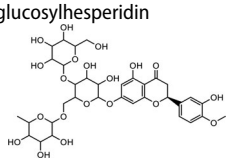
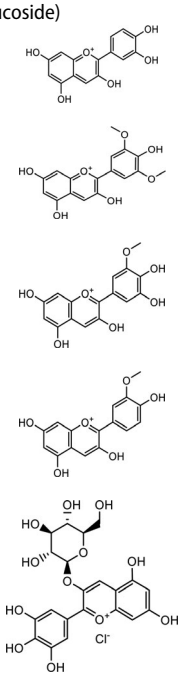
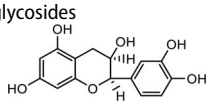
and lipopolysaccharide (LPS) which facilitates the progression of arthritis (Luczkiewicz et al. 2014). Liu and coworkers showed the anti-rheumatoid arthritis activity of Astraglus in AIA rats by modulating RANKL/NF/osteoprotegerin (OPG) pathways. Total flavonoids of astraglus (TFA) extracted from *Astragalus membranaceus* Bunge, was administered in CIA rats with a dose of 25, 50, 100 mg/kg daily for 28 days. ELISA assay and immunochemical method were performed to examine the inflammatory mediators. After the intervention for 28 days, TFA suppressed the production and activation of RANKL, PG E2, TNF-α, and IL-1β and facilitated the production of OPG. Additionally, TFA gradually reduced the formation of pannus, synovial hyperplasia, and inflammatory cell infilteration as well as bone and cartilage destruction (Liu et al. 2017). A study performed by Ananth, showed the anti-rheumatic effects of Pergularia doemia methanolic extract (PDME) obtained from *Pergularia doemia* in CFA induced arthritis rats. Results exhibited that the administration of PDME significantly ameliorated the bone destruction by suppressing the swelling and inflammation in joints. In addition, PDME treatment also reduced the levels of rheumatoid factor (RF), white blood cells (WBC), CRP and ESR while increased the levels of red blood cell (RBC) and hemoglobin (Ananth et al. 2016). Vetal and coworkers examined the anti-arthritic effects of type-A procyanidine polyphenols (TAPP) by *cinnamomum zeylanicum* in AIA and carrageena induced paw edema rats. Study revealed that the administration of TAPP with a dose of 8 mg/kg daily for 9 days reduced the arthritic score, cachexia, CRP and ankle diameter (Vetal et al. 2013).

Naringin, a dietary flavanone, extracted from numerous citrus fruits and grapes, exerts various therapeutic activities including antitussive activity, an expectorant action, antiasthematic and used for lungs injuries. Wang and colleagues investigated the anti-arthritic effects of naringin by using AIA rat model. Rats were randomly divided into four groups: 1st group- AA + naringin (20 mg/kg), 2nd group- AA + naringin (40 mg/kg), 3rd group- control group and 4th group- AA + dexamethasone (2 mg/kg). After the intervention for 28 days, both narignin treated group suppressed the formation of IL-6, IL-1β, Bcl-2 and TNF-α whereas enhanced the production of Bax. Thus, both dose of naringin reduced the symptoms and have potential therapeutic effect in rheumatoid arthritis (Wang et al. 2015). A study analyzed the efficacy of theaflavin-3,3-digallate (TFDG), extracted from black tea polyphenol, on osteoclast and MMP activity by using mature osteoclasts and osteoclast precursor cells. The administration of TFDG at a dose of 10 and 100 μM for 7 days, gradually reduced the formation of osteoclast via downregulating MMP-2 and MMP-9 expressions (Oka et al. 2011). A study conducted by Liu et al. examined the anti-arthritic efficacy of TFDG by using CIA rat model. The occurrence of arthritis and arthritis score were evaluated. ELISA and western blotting essay were also performed to assess the expression of pro-inflammatory mediators. Results revealed that the treatment of TFDG with a dose 10 mg/kg, 3 times/week for 9 weeks, significantly reduced the expression of arthritis score, TNF-α, MMP-1, IL-1β, IL-6, MMP-2, MMP-3, ERK, JNK2, P38, NF-κB and MAPK signaling pathway (Liu and Li 2019). A study conducted by Umar et al., evaluated the anti-rheumatic activity of thymoquinone, derived from *vigella sativa*, on RAFLS. Results showed that the administration of thymoquinone (1–5 μM) for 2 h, reduced the expression of IL-8, IL-6, ICAM-1, Cad-11, p-38, VCAM-1 and JNK (Umar et al. 2015). Furthermore, another study conducted by Tekeoglu et al. also supports the anti-inflammatory effects of thymoquinone in CIA rat model. After the administration of 2.5 mg/kg for 5 days, thymoquinone suppressed the formation of IL-1β (Tekeoglu et al. 2007). Vaillancourt et al. also analyzed the anti-rheumatic effects of thymoquinone by using human RAFLS and AIA rat models. Study revealed that administration of thymoquinone at a dose of 10, 5, 2 and 1 μM for 1 h in human RAFLS, significantly suppressed the FSL proliferation, TNF-α, IL-1β, COX-2, prostaglandins and MMP-13 which were induced by liposaccharides and also reduced p-p-38-MKK, P-NF-κB-p-65, p-ERK and 4-hydroxynonenal (HNE) which were induced by H_2O_2. In addition, when it was administered with a dose of 5 mg/kg in AIA rats for 24 h, gradually downregulated the expressions of HNE, TNF-α and IL-1β (Vaillancourt et al. 2011). Another study analyzed the anti-arthritic activity of ethyl ether and ethyl acetate extract of polygonum orientale (POEe and POEa) extracted from *Polygonum orientale* L. (polygonaceae) by using AIA rat model. ELISA assay was performed to evaluate the levels of pro-inflammatory mediators. Results revealed that POEe and POEa gradually decreased the clinical manifestations of rheumatoid arthritis by suppressing arthritis score, spleen and thymus indices and swelling in joints. Instantaneously, these agents also decreased the levels of TNF-α, IL-1β and PG E2. A significant reduction in synovial hyperplasia, bone erosion, cartilage destruction, joint degeneration and inflammation cell infiltration was also observed after the treatment of POEe and POEa (Gou et al. 2018) (Table 3).

Other polyphenolic compounds

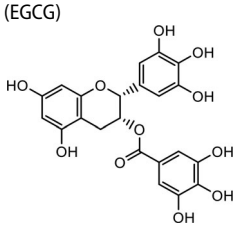
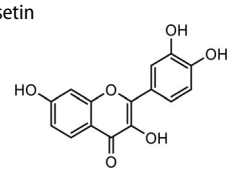
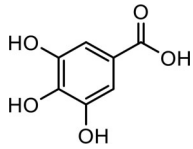
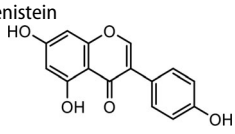
Recent studies have been reported the anti-inflammatory effects of extra virgin olive oil (EVOO) containing high contents of polyphenolic compounds. Depending upon anti-inflammatory action of EVOO, Rosillo et al. analyzed the anti-rheumatic actions by using CIA model. The extracts of EVOO-polyphenol with a dose of 100 and 200 mg/kg was administered for 13 days in CIA rats. Results revealed that the treatment of EVOO polyphenol extract significantly reduced the cell migration, bone erosion, cartilage degradation and joint edema. Additionally, it also exerted anti-rheumatic effects by downregulating the expression of IL-1β, TNF-α, PGE2, JNK, 1κB-α and p-65 (Rosillo et al. 2014). Another study examined the anti-rheumatic efficacy of hydroxytyrosol (HTy-Ac), derived from EVOO, by using CIA model. The study demonstrated that the treatment of HTy-Ac significantly reduced the serum MMP-3, IgG2a, IgG1, COMP, IL-1R, IFN-S, IL-6, IL-17A, TNF-Q, MAPKs, JAK/STAT and NF-κB. While it upregulated hemeoxygenase-1

Table 3. Suppression of rheumatoid arthritis by flavonoids.

Source	Compound	Dose/Duration	Animal model/ cell Line	Mechanism	References
Pergularia domenia	Pergularia domenia metanolic extract	500 mg/kg for 20 days	CFA-RA rat	↓ bone destruction, WBC, CRP, ESR ↑ RBC, hemoglobin	Ananth et al. (2016)
Astragalus membranaceus	Astragalus (Formononetin, Formononetin-7-O-β-D-glucopyronoside, Calycosin, Calycosin-7-O-β-D-glucopyronoside) 	25/50/100 mg/kg/ day/28 days	CIA rat	↓ RANK, PG E2, TNF-α, IL-1β	Liu et al. (2017)
Citrus fruit	A-glucosylhesperidin 	3 mg/0.3 ml thrice a week,31 days	CIA rat	↓ TNF-α	Kometani et al. (2008)
Cherries	Anthocyanin(cyanidin, malvidin, petunidin, peonidin, delphinidin-3-glucoside) 	10, 20, 40 mg/ kg/14 days	AIA rat	↓ PGE2, TNF-α, MDA ↑ SOD	He et al. (2006)
Cocoa	Epicatechin, procyanidin, catchins and flavonol glycosides 	0, 10, 20 μM/mL/1 h	Mouse epidermal cells and Jb6 P	↓ NF-κB, VEGF, AP-1 ↑ p-ERK, p-Akt, p-MKK4, p-P70S6K, p-p90RSK, p-PI3K, p-JNK	Kim et al. (2010)

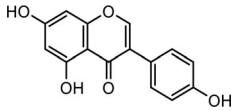
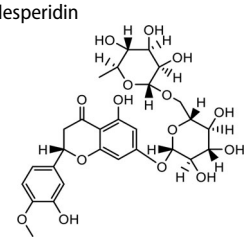
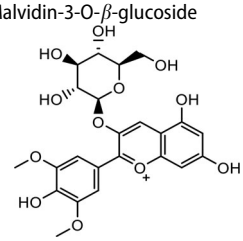
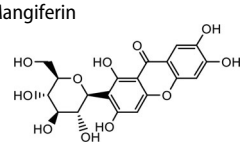
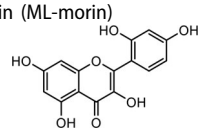
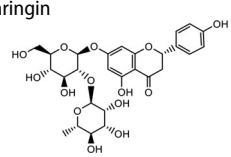
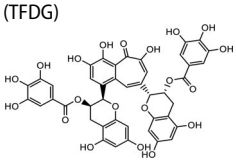
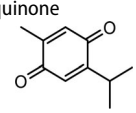
(*continued*)

Table 3. Continued.

Source	Compound	Dose/Duration	Animal model/ cell Line	Mechanism	References
Camellia sinensis	Epigallocatechin-3-gallate (EGCG) 	10, 20, 30, 40, 50 mg/ kg/3 weeks	RASFs	↓ RANTES, MMP-2, ENA-78, GRO-α	Ahmed, Pakozdi, and Koch (2006)
Green tea	Epigallocatechin-3-gallate (EGCG)	10 mg/kg/5 days	CIA rat	↓ IL-6, IL-1β, IL-17, TNF-α, CTSK, c-FOS, p-STAT727, IL-21, p-ERK, p-STAT3, p-STAT3 705, RANK, AHR, iNOS, CCL6, IgG2a, TRAP, CTR, nitrotyrosine, VEGF, NFATc1, MMP9 ↑ TGF-β, Foxp3, IL-10, SOCS3	Lee et al. (2007)
Green tea	Epigallocatechin gallate	20 μM, 50 μM/15 days	PIA rat	↓ MPO	Leichsenring et al. (2016)
Camellia sinensis	Epigallocatechin-3-gallate (EGCG)	10 mg/kg/3 weeks	1. DBA/1 mice 2. Human osteoclast (peripheral blood monocytes)	↓ carbonic anhydrase II, NFATc1, cathepsin K, β-3 integrin, CTR, α-v integrin	Morinobu et al. (2008)
Green tea	Epigallocatechin-3-gallate (EGCG)	10,100 μM/7 days	CIA rat	↓ INF-γ, IL-6, TNF-α ↑ anti-CII specific IgG1 antibodies	Min et al. (2015)
Camellia sinensis	Epigallocatechin-3-gallate (EGCG)	125, 250, 500 nM/24 h	Osteoclast precursors cells mature osteoclast	↓ MMP-2, MMP-9	Oka et al. (2011)
Camellia sinensis	Epigallocatechin-3-gallate (EGCG)	125, 250, 500 nM/24 h	RASFs	↓ MMP-1, MAPK, AP-1, MMP-3, p-p-38, p-JNK, p-ERK1/2	Yun et al. (2008)
Green tea	Epigallocatechin-3-gallate (EGCG)	25/50/mg/kg for 3 weeks	γKO & CIA rat	↓ arthritis score, IL-6, VEGF, IL-17, IL-1β, TNF-α, nitrotyrosine, iNOS, PSAT3 705/727	Lee et al. (2009)
Green tea	Epigallocatechin-3-gallate (EGCG)	40 mg/kg, thrice a week	IL-1RaKO model	↓ PSTAT3 705/723, HIF-1α, mTOR, IgG2a	Yang et al. (2014)
Rhus verniflura Stokes	Fisetin 	0.1, 1, 10 μM/mL/72 h	RA FLs	↓ IL-6, MAPK, VEGF, TNF-α, IL-8	Lee et al. (2016)
Rhus verniflura Stokes	Flavonol-rich residual layer of hexane fraction	0.1, 1, 10 μM/mL/72 h	RA FLs	↓ p-JNK, p-ERK ↑ p-p38-MAPK	Lee et al. (2016)
Cinnamomum zeylanicum	Gallic acid 	1. 200 mg/ kg/12 days 2. 40 μM/ 100 μL/72 h	1. AIA rats 2. Concanavalin stimulated lymphocyte	1. ↓ TNF-α 2. ↓ IL-4, IFN-γ, IL-2	Rathi et al. (2013)
Soybean	Genistein 	1 mL/kg/42 days	CIA rat	↓ Th1/Th2, IFN-γ, T-bet Increase IL-4, GATA-3	Wang et al. (2008)

(*continued*)

Table 3. Continued.

Source	Compound	Dose/Duration	Animal model/ cell Line	Mechanism	References
Soybean	Genistein 	10 μg/mL/22 days	RA FLS	↓ MMP-9	Zhang et al. (2012)
Soybean	Hesperidin 	160 mg/kg/22 days	CIA rat	↓ nitrite, ELA, TBARS	Umar et al. (2013)
Red grapes	Malvidin-3-O-β-glucoside 	1. 1,10,100 μM/24 h 2. 25 mg/ kg/10 days	1. Peripheral monocyte-derived macrophages 2. Peritoneal macrophages 3. AIA rats	1. ↓ IL-1, IL-6, IL-8, NOx, NO, MIP1a, TNF-α 2. ↓ IL-8, IL-1β, TNF-α	Decendit et al. (2013)
Thymelaeaceae family	Mangiferin 	100 and 400 mg/kg for14 days and 27 days	CIA rat	↓ IL-6, TNF-α, NF-κB, RANKL, IL-1β, ERK1/2	Tsubaki et al. (2015)
Tea, vegetables and fruits	Morin (ML-morin) 	10 mg/kg for 3 days	Spleen and synovial macrophages	↓ NO, ROS, TNF-α, iNOS, IL-6, NF-κB-p-65, IL-1β, MCP-1, STAT-3, RANKL, VEGF	Sultana, Neog, and Rasool (2017)
Swertia chirayita	Mangiferin	23.72 mg/kg for 12 days	AIA rat	↓ IL-1, TNF-α, TNF-γ ↑ IL-10	Kumar et al. (2004)
Cinnamomum zelanicum	Procyanidine (catechin and epicatechin)	8 mg/kg/day for 9 days	AIA rat	↓ arthritis score, cachexia, CRP	Vetal et al. (2013)
Citrus fruits and grapes	Naringin 	1. 20 mg/kg for 28 days 2. 40 mg/kg for 28 days	AIA rat	↓ IL-6, TNF-α, Bcl-2, IL-1β Increase Bax	Wang et al. (2015)
Camellia sinensis	Theaflavin-3,3′-digallate (TFDG) 	10, 100 μM for 7 days	Osteoclast precursors cell mature osteoclast	↓ MMP-2, MPP-9, osteoclast formation	Oka et al. (2011)
Black tea	Theaflavin-3,3′-digallate (TFDG)	10 mg/kg/ 3 times/ weak for 9 days	CIA rat	↓ TNF-α, MMP-1, IL-1β, IL-6, MMP-2, MMP-3, ERK, JNK2, P38, NF-κB, MAPK	Liu and Li (2019)
Nigella sativa	Thymoquinone 	10, 100 μM for 7 days	RA synovium	↓ p-38, JNK, Cad-11, IL-6, ICAM-1, IL-8, VCAM-1	Umar et al. (2015)

(*continued*)

Table 3. Continued.

Source	Compound	Dose/Duration	Animal model/ cell Line	Mechanism	References
Nigella sativa	Thymoquinone	2.5 mg/kg for 5 days 5 mg/kg for 5 days 1, 2, 3, 4, 5 μM for 2 h	CIA rat	↓ IL-1β	Tekeoglu et al. (2007)
Nigella sativa	Thymoquinone	1. 0, 1, 5, 10 μM for 1 h 2. 5 mg/kg for 1 day	1. RA FLS 2. AIA rat	1. ↓ TNF-α, COX-2, HNE, p-ERK, p-p-38-MKK, prostaglandins, IL-1β, p-NF-κB-p65, MMP-13 2. ↓ IL-1β, HNE, TNF-α	Vaillancourt et al. (2011)
Polygonum orientale (P.O.)	Ethyl ether and ethyl acetate extract of P.O	3.75/5/7.5 mg/kg/day for 26 days	AIA rat	↓ TNF-α, IL-1β, PG E2	Gou et al. (2018)

VEGF: vascular endothelial growth factor; ENA-78: Epithelial neutrophil-activating protein78; HNE: H2O2-induced 4-hydroxynonenal; ICAM: intercellular adhesion molecules; GRO: growth-regulated oncogene; RAFLS: RA fibroblast-like synoviocytes; VCAM: vascular cell adhesion protein; MKK: mitogen-activated protein kinase kinase4; LPS: lipopolysaccharides; RANTES: regulated on activation, normal t-cell expressed and secreted; LPS: lipopolysaccharides; RBC: red blood cells.

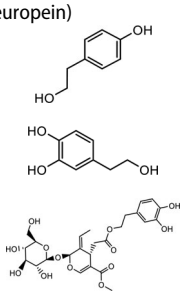
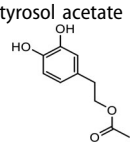
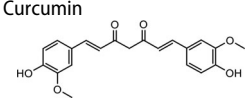
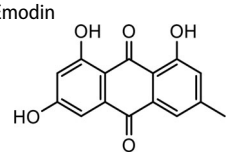
(HO-1) protein and nuclear factor E-2 related factor 2 (Nrf2) expressions (Rosillo et al. 2015). Ramadan et al. performed a comparative study to examine the potency of curcuminoids (Turmeric) and gingnols and shogaols (Ginger) rhizomes in AIA rats. Results revealed that the intervention of both extracted compounds (200 mg/kg) for 28 days significantly reduced the severity and incidence of rheumatoid arthritis by decreasing the pro-inflammatory cytokines and increasing anti-inflammatory activity. Additionally, the administration of turmeric polyphenolic compounds showed higher anti-rheumatic action than ginger and indomethacin by suppressing alanine transaminase, alkaline phosphate and lipid peroxidation (Ramadan, Al-Kahtani, and El-Sayed 2011). Kloesch et al. examined the antiapoptotic and anti-inflammatory effects of curcumin polyphenol on RA-FLS and human synovial fibroblast cell line. Receptor gene, western bottling and ELISA assay were performed to analyze the expressions of NF-κB, p38, IL-1, VEGF, MAPK and ERK1/2 mediators. Results revealed that the treatment of curcumin at a dose of 50, 25, 12.5 μM, significantly suppressed the expression of IL-6, IL-1β and VEGF in both RA-FLS and synovial fibroblast cell line. Furthermore, curcumin blocked the dephosphorylation of ERK1/2 and activation of NF-κB. In addition, administration of high dose of curcumin reduce the induction of apoptosis and cell viability (Kloesch et al. 2013). A randomized clinical trial was conducted by Chandran et al. showed the antiarthritic and anti-inflammatory activity of curcumin in 45 subjects having rheumatoid arthritis. 1st group was treated curcumin (500 mg), 2nd group was treated diclofenac sodium (50 mg) and 3rd group was treated with both diclofenac sodium and curcumin. A significant reduction in swelling and arthritis score was observed in all these treated group but curcumin treated group exhibited a remarkable improvement in reduction of arthritis symptoms. Moreover, curcumin did not showed any adverse effects and marked to be safe. Thus, both the studies support the curcumin polyphenol to be used as a potent therapeutic agent in the management of rheumatoid arthritis (Chandran and Goel 2012).

Park et al. examined the anti-rheumatic effects of curcumin, derived from *curcuma longa* rhizomes, in synovial fibroblast. Fluorescent microscopy, Annexin-V-based assay and MTT assay was performed to analyzed the anti-RA effects. Study revealed that the treatment of curcumin with cells at a dose of 25, 50, 75 and 100 μm for 24 h, repressed the expressions of caspase-3, ADP-ribose, caspase-9, COX-2 and Bcl-2 (Park et al. 2007). Curcumin, derived from herb turmeric ameliorated the clinical symptoms of RA by suppressing TNF-α, IL-1β and TNF-κB in CIA model when it was treated with 50 mg/kg for 24 h. Emodin (3 methyl-1,6,8-trihydroxyanthraquinone) derived from *Rheum Palmatum* has attained various beneficial effects on human health including antibacterial, vasorelaxant, diuretic and antitumor. Hwang et al. conducted an experiment on CIA mice model to investigate the arthritis-modulating efficacy of emodin. After 11 days intervention of emodin (10 mg/kg), repression in expressions of MMP, M-CSF and NF-κB pathway were observed (Hwang et al. 2013). Another study conducted by Zhu and colleagues also reported anti-rheumatic action of emodin. Study revealed that the administration of emodin with a dose of 20, 10, and 5 mg/kg for 21 days in CIA rats, reduced the release of TNF-α, PGE2, COX and IL-6 (Zhu et al. 2013). On human RA synoviocytes, emodin also demonstrated identical effects by alleviating VEGF, COX-2, histone deacetylase (HDAC), HDAC1, hypoxia induced factor 1 alpha(HIF-1α), MPP-13, MMP-1, MAPK and NF-κB (Ha et al. 2011) (Table 4).

Conclusion

Chronic diseases can be well treated with the medication which have been tendency to alter the inflammatory pathways. In plants, the bioactive compounds known as polyphenols, can be used as prophylaxis as well as in the management of certain diseases. Many extract or even remote phenolic compounds have been obtained from various variety of plants, which have shown their efficacy toward autoimmune diseases in preclinical and clinical studies. The pathology of rheumatoid arthritis have been alter by the natural phenolic extract as they modulate the formation and mechanism of action of inflammatory mediators. The

Table 4. Suppression of rheumatoid arthritis by other polyphenolic compounds.

Source	Compound	Dose/Duration	Animal model/ cell Line	Mechanism	References
EVOO	EVOO polyphenol extract (tyrosol, hydroxytyrosol, oleuropein) 	100, 200 mg/kg for 13 days	CIA rat	↓ p-38, IL-6, JNK, TNF-α, PGE2, p-65, IL-1β	Rosillo et al. (2014)
EVOO	Hydroxytyrosol acetate 	0.05% for 42 days	CIA rat	↓ IL-6, IL-1R, COMP, TNF-Q, IgG1, MMP-3, IgG2a, Nrf-2, IL-17A, HO-1, IFN-S	Rosillo et al. (2015)
1. Turmeric rhizome 2. Ginger rhizome	Curcuminoid	200 mg/kg for 28 days	AIA rat	↓ ALP, LPO, ALAT ↑ IL-1β, IL-4, IL-6, SOD, IL-10, GSH, CAT, TNF-α	Ramadan, Al-Kahtani, and El-Sayed (2011)
Turmeric rhizome	Curcumin 	12.5, 25, 50 μM for 6 h	1. MH7A 2. RA FLS	1. ↓ IL-6, IL-1β, AP-1, NF-κB, ERK1/2↑ LDH 2. ↓ NF-κB, VEGF-A, IL-6, AP-1, ERK1/2, IL-1β	Kloesch et al. (2013)
Turmeric rhizome	Curcumin	500 mg, twice daily for 8 weeks	Subjects with arthritis	↓ swelling, inflammation, arthritis score	Chandran& Goel (2012)
Herb turmeric	Curcumin oil water (nanoemulsion)	50 mg/kg for 14 days	AIA rat	↓ IL-1β, NF-κB, TNF-α	Zhang et al. (2016)
Curcuma longa rhizome	Curcumin	0, 25, 50, 75, 100 μM for 24 h	FLS or patients	↓ COX-2, Bcl-2 ↑ caspase-9, caspase-3	Park et al. (2007)
Rheum palmatum	Emodin 	10 mg/kg for 11 days	CIA rat	↓ MMP, NF-κB, M-CSF	Hwang et al. (2013)
Rheum palmatum	Emodin	5, 10, 20 mg/kg for 21 days	CIA rat	↓ PGE2, TNF-α, IL-6	Zhu et al. (2013)
Rheum palmatum	Emodin	0.1, 1, 10 μM for 24 h	Synovial membrane/ Humans	↓ COX-2, MMP-13, HDAC, HIF-1a, HDAC1, VEGF, MMP-1, MAPK, NF-κB	Ha et al. (2011)

M-CSF: macrophage colony-stimulating factor; HO-1: hemeoxygenase1; HIF: hypoxia-inducible factor; LDH: lactate dehydrogenase; ALAT: alanine transaminase; MH7A: rheumatoid synovial cell; LPO: lipid peroxidation; HDAC: histone deacetylase; ALP: alkaline phosphatase; Nrf2: nuclear factor(erythroid-derived2)-like2.

clinical manifestation of rheumatoid arthritis can be ameliorated by these secondary metabolites through suppression of various mediators such as JNK, IL-6, AP-1, TNF-α, COX-2, MAPK, ERK1/2 and NF-κB. Polyphenols exhibit anti-rheumatoid arthritis characteristics by directly modifying the inflammatory pathways. However, to depict the exact molecular mechanism of polyphenols which regulate pathogenic pathways of rheumatoid arthritis, many preclinical and clinical trials could be conducted. Despite of having unknown mechanism, polyphenols could be the near future ideal therapeutic in the treatment of autoimmune diseases.

Future prospects

Noticeable progress has been made in investigating and exploring the role of polyphenolic compounds and their significance in ameliorating the progression of RA. However, there should be a more extensive exploration of the microbial metabolism of polyphenols, because of their limited absorption profile and gut microbiome-mediated degradation in the colon. The microbial metabolites of dietary polyphenols are responsible for their biological action. Therefore, the future researches and studies should target

this parameter of polyphenolic research. Furthermore, the relationship between gut microbiome and polyphenols should be evaluated for its impact in the development and progression of RA. For instance, the growth of beneficial bacteria, like *Bifidobacterium* and *Lactobacillus* is elevated by intake of numerous polyphenols, however, their intake has been found to curb the growth of *Firmicutes*. Polyphenols have also been found to exert a positive impact on the composition of gut microbiome, thereby, regulating host immunity. Thus, polyphenol investigations in future should focus on the role of gut microbiome, in affecting the polyphenol ability to treat RA complications. Clinical in vivo and in vitro investigations have demonstrated altered levels of cytokines and appearance of bone lesions in RA. Thus, future experimentation in RA can focus on investigating the natural compounds, acting on more than one targets that would possibly exert a positive effect in RA treatment. The research paradigm associated with natural phytochemicals can be further modified by investigating the efficacy of nanocarrier formulations of such compounds, which has been found to enhance the beneficial impact of natural compounds and mitigate the weak pharmacokinetic profile of natural drugs, which might aid in the evolution phytochemical industry in the pharmaceutical paradigm. Also, well-organized clinical trials with optimized design has become necessary, in order to investigate the therapeutic potential of polyphenolic agents in RA.

Acknowledgements

The authors want to thank Chitkara College of Pharmacy, Chitkara University, Punjab, India for providing resources for completion of the current article.

Disclosure statement

The authors declare no conflict of interest, financial or otherwise.

ORCID

Amirhossein Ahmadi http://orcid.org/0000-0002-9737-3633

References

Ahmed, S., A. Pakozdi, and A. E. Koch. 2006. Regulation of interleukin-1β–induced chemokine production and matrix metalloproteinase 2 activation by epigallocatechin-3-gallate in rheumatoid arthritis synovial fibroblasts. *Arthritis & Rheumatism* 54 (8):2393–401. doi: 10.1002/art.22023.

Ahn, S.-C., G.-Y. Kim, J.-H. Kim, S.-W. Baik, M.-K. Han, H.-J. Lee, D.-O. Moon, C.-M. Lee, J.-H. Kang, B.-H. Kim, et al. 2004. Epigallocatechin-3-gallate, constituent of green tea, suppresses the LPS-induced phenotypic and functional maturation of murine dendritic cells through inhibition of mitogen-activated protein kinases and NF-κB. *Biochemical and Biophysical Research Communications* 313 (1):148–55. doi: 10.1016/j.bbrc.2003.11.108.

An, Q., W. Yan, Y. Zhao, and K. Yu. 2018. Enhanced neutrophil autophagy and increased concentrations of IL-6, IL-8, IL-10 and MCP-1 in rheumatoid arthritis. *International Immunopharmacology* 65:119–28. doi: 10.1016/j.intimp.2018.09.011.

Ananth, D. A., A. Rameshkumar, R. Jeyadevi, G. S. B. Aseervatham, J. Sripriya, P. C. Bose, and T. Sivasudha. 2016. Amelioratory effect of flavonoids rich Pergularia daemia extract against CFA induced arthritic rats. *Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie* 80:244–52. doi: 10.1016/j.biopha.2016.03.019.

Ayissi, V., A. Ebrahimi, and H. Schluesenner. 2014. Epigenetic effects of natural polyphenols: A focus on SIRT1-mediated mechanisms. *Molecular Nutrition & Food Research* 58 (1):22–32. doi: 10.1002/mnfr.201300195.

Bathon, J. M., R. W. Martin, R. M. Fleischmann, J. R. Tesser, M. H. Schiff, E. C. Keystone, M. C. Genovese, M. C. Wasko, L. W. Moreland, A. L. Weaver, et al. 2000. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *New England Journal of Medicine* 343 (22):1586–93. doi: 10.1056/NEJM200011303432201.

Belwal, T., H. P. Devkota, H. A. Hassan, S. Ahluwalia, M. F. Ramadan, A. Mocan, and A. G. Atanasov. 2018. Phytopharmacology of Acerola (Malpighia spp.) and its potential as functional food. *Trends in Food Science & Technology* 74:99–106. doi: 10.1016/j.tifs.2018.01.014.

Betancourt, B. Y., A. Biehl, J. D. Katz, and A. A. Subedi. 2018. Pharmacotherapy pearls in rheumatology for the care of older adult patients: Focus on oral disease-modifying antirheumatic drugs and the newest small molecule inhibitors. *Rheumatic Diseases Clinics of North America* 44 (3):371–91. doi: 10.1016/j.rdc.2018.03.010.

Bouayed, J. 2010. Polyphenols: A potential new strategy for the prevention and treatment of anxiety and depression. *Current Nutrition & Food Science* 6 (1):13–8. doi: 10.2174/157340110790909608.

Bowie, A., and L. A. O'Neill. 2000. Oxidative stress and nuclear factor-kappaB activation: A reassessment of the evidence in the light of recent discoveries. *Biochemical Pharmacology* 59 (1):13–23. doi: 10.1016/s0006-2952(99)00296-8.

Boyanapalli, S. S., and A. N. T. Kong. 2015. "Curcumin, the king of spices": Epigenetic regulatory mechanisms in the prevention of cancer, neurological, and inflammatory diseases. *Current Pharmacology Reports* 1 (2):129–39. doi: 10.1007/s40495-015-0018-x.

Busch, F., A. Mobasheri, P. Shayan, C. Lueders, R. Stahlmann, and M. Shakibaei. 2012. Resveratrol modulates interleukin-1β-induced phosphatidylinositol 3-kinase and nuclear factor κB signaling pathways in human tenocytes. *Journal of Biological Chemistry* 287 (45):38050–63. doi: 10.1074/jbc.M112.377028.

Camporeale, A., and V. Poli. 2012. IL-6, IL-17 and STAT3: a holy trinity in auto-immunity?

Capiralla, H., V. Vingtdeux, H. Zhao, R. Sankowski, Y. Al-Abed, P. Davies, and P. Marambaud. 2012. Resveratrol mitigates lipopolysaccharide- and Aβ-mediated microglial inflammation by inhibiting the TLR4/NF-κB/STAT signaling cascade. *Journal of Neurochemistry* 120 (3):461–72. doi: 10.1111/j.1471-4159.2011.07594.x.

Castro-Acosta, M. L., G. N. Lenihan-Geels, C. P. Corpe, and W. L. Hall. 2016. Berries and anthocyanins: Promising functional food ingredients with postprandial glycaemia-lowering effects. *Proceedings of the Nutrition Society* 75 (3):342–55. doi: 10.1017/S0029665116000240.

Chandran, B., and A. Goel. 2012. A randomized, pilot study to assess the efficacy and safety of curcumin in patients with active rheumatoid arthritis. *Phytotherapy Research: PTR* 26 (11):1719–25. doi: 10.1002/ptr.4639.

Christman, L., and L. Gu. 2020. Efficacy and mechanisms of dietary polyphenols in mitigating rheumatoid arthritis. *Journal of Functional Foods* 71:104003. doi: 10.1016/j.jff.2020.104003.

Chuang, D. Y., A. Simonyi, J. Cui, D. B. Lubahn, Z. Gu, and G. Y. Sun. 2016. Botanical polyphenols mitigate microglial activation and microglia-induced neurotoxicity: Role of cytosolic phospholipase A2. *Neuromolecular Medicine* 18 (3):415–25. doi: 10.1007/s12017-016-8419-5.

Coussens, L. M., and Z. Werb. 2002. Inflammation and cancer. *Nature* 420 (6917):860–7. doi: 10.1038/nature01322.

Crofford, L. J. 2013. Use of NSAIDs in treating patients with arthritis. *Arthritis Research & Therapy* 15 (S3):S2. doi: 10.1186/ar4174.

Dahan, S., Y. Segal, and Y. Shoenfeld. 2017. Dietary factors in rheumatic autoimmune diseases: A recipe for therapy? *Nature Reviews Rheumatology* 13 (6):348–58. doi: 10.1038/nrrheum.2017.42.

de Villiers, A., P. Venter, and H. Pasch. 2016. Recent advances and trends in the liquid-chromatography-mass spectrometry analysis of flavonoids. *Journal of Chromatography A* 1430:16–78. doi: 10.1016/j.chroma.2015.11.077.

Decendit, A., M. Mamani-Matsuda, V. Aumont, P. Waffo-Teguo, D. Moynet, K. Boniface, E. Richard, S. Krisa, J. Rambert, J.-M. Mérillon, et al. 2013. Malvidin-3-O-β glucoside, major grape anthocyanin, inhibits human macrophage-derived inflammatory mediators and decreases clinical scores in arthritic rats. *Biochemical Pharmacology* 86 (10):1461–7. doi: 10.1016/j.bcp.2013.06.010.

Ding, S., H. Jiang, and J. Fang. 2018. Regulation of immune function by polyphenols. *Journal of Immunology Research* 2018:1–8. doi: 10.1155/2018/1264074.

Direito, R., J. Rocha, B. Sepodes, and M. Eduardo-Figueira. 2021. Phenolic compounds impact on rheumatoid arthritis, inflammatory bowel disease and microbiota modulation. *Pharmaceutics* 13 (2):145. doi: 10.3390/pharmaceutics13020145.

Donahue, H. J., R. W. Qu, and D. C. Genetos. 2018. Joint diseases: From connexins to gap junctions. *Nature Reviews Rheumatology* 14 (1):42–51. doi: 10.1038/nrrheum.2017.204.

Doss, H. M., S. Samarpita, R. Ganesan, and M. Rasool. 2018. Ferulic acid, a dietary polyphenol suppresses osteoclast differentiation and bone erosion via the inhibition of RANKL dependent NF-κB signalling pathway. *Life Sciences* 207:284–95. doi: 10.1016/j.lfs.2018.06.013.

Dreiseitel, A., G. Korte, P. Schreier, A. Oehme, S. Locher, G. Hajak, and P. G. Sand. 2009. sPhospholipase A 2 is inhibited by anthocyanidins. *Journal of Neural Transmission* 116 (9):1071–7. doi: 10.1007/s00702-009-0268-z.

Du, G.-J., Z. Zhang, X.-D. Wen, C. Yu, T. Calway, C.-S. Yuan, and C.-Z. Wang. 2012. Epigallocatechin gallate (EGCG) is the most effective cancer chemopreventive polyphenol in green tea. *Nutrients* 4 (11):1679–91. doi: 10.3390/nu4111679.

El Khawand, T., A. Courtois, J. Valls, T. Richard, and S. Krisa. 2018. A review of dietary stilbenes: Sources and bioavailability. *Phytochemistry Reviews* 17 (5):1007–29. doi: 10.1007/s11101-018-9578-9.

Figueira, I., R. Menezes, D. Macedo, I. Costa, and C. Nunes dos Santos. 2017. Polyphenols beyond barriers: A glimpse into the brain. *Current Neuropharmacology* 15 (4):562–94. doi: 10.2174/1570159X14666161026151545.

Frantz, M. C., and P. Wipf. 2010. Mitochondria as a target in treatment. *Environmental and Molecular Mutagenesis* 51 (5):462–75. doi: 10.1002/em.20554.

Gabriel, S. E. 2001. The epidemiology of rheumatoid arthritis. *Rheumatic Diseases Clinics of North America* 27 (2):269–81. doi: 10.1016/s0889-857x(05)70201-5.

Ganesan, K., and B. Xu. 2017. A critical review on polyphenols and health benefits of black soybeans. *Nutrients* 9 (5):455.

Gou, K.-J., R. Zeng, X.-D. Ren, Q.-L. Dou, Q.-B. Yang, Y. Dong, and Y. Qu. 2018. Anti-rheumatoid arthritis effects in adjuvant-induced arthritis in rats and molecular docking studies of Polygonum orientale L. extracts. *Immunology Letters* 201:59–69. doi: 10.1016/j.imlet.2018.11.009.

Grootaert, C., S. Kamiloglu, E. Capanoglu, and J. V. Camp. 2015. Cell systems to investigate the impact of polyphenols on cardiovascular health. *Nutrients* 7 (11):9229–55. doi: 10.3390/nu7115462.

Ha, M.-K., Y. H. Song, S.-J. Jeong, H.-J. Lee, J. H. Jung, B. Kim, H. S. Song, J.-E. Huh, and S.-H. Kim. 2011. Emodin inhibits proinflammatory responses and inactivates histone deacetylase 1 in hypoxic rheumatoid synoviocytes. *Biological & Pharmaceutical Bulletin* 34 (9):1432–7. doi: 10.1248/bpb.34.1432.

Haleagrahara, N., K. Hodgson, S. Miranda-Hernandez, S. Hughes, A. B. Kulur, and N. Ketheesan. 2018. Flavonoid quercetin-methotrexate combination inhibits inflammatory mediators and matrix metalloproteinase expression, providing protection to joints in collagen-induced arthritis. *Inflammopharmacology* 26 (5):1219–32. doi: 10.1007/s10787-018-0464-2.

Haleagrahara, N., S. Miranda-Hernandez, M. A. Alim, L. Hayes, G. Bird, and N. Ketheesan. 2017. Therapeutic effect of quercetin in collagen-induced arthritis. *Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie* 90:38–46. doi: 10.1016/j.biopha.2017.03.026.

Harris, J. 2011. Autophagy and cytokines. *Cytokine* 56 (2):140–4. doi: 10.1016/j.cyto.2011.08.022.

He, Y., H. Zeng, Y. Yu, J. Zhang, X. Zeng, F. Gong, X. Duan, Q. Liu, and B. Yang. 2017. Resveratrol improved the progression of chronic prostatitis via the downregulation of c-kit/SCF by activating Sirt1. *Journal of Agricultural and Food Chemistry* 65 (28):5668–73. doi: 10.1021/acs.jafc.7b01879.

He, Y.-H., J. Zhou, Y.-S. Wang, C. Xiao, Y. Tong, J. C.-O. Tang, A. S.-C. Chan, and A.-P. Lu. 2006. Anti-inflammatory and anti-oxidative effects of cherries on Freund's adjuvant-induced arthritis in rats. *Scandinavian Journal of Rheumatology* 35 (5):356–8. doi: 10.1080/03009740600704155.

Hong, K.-S., J.-I. Park, M.-J. Kim, H.-B. Kim, J.-W. Lee, T. T. Dao, W. K. Oh, C.-D. Kang, and S.-H. Kim. 2012. Involvement of SIRT1 in hypoxic down-regulation of c-Myc and β-catenin and hypoxic preconditioning effect of polyphenols. *Toxicology and Applied Pharmacology* 259 (2):210–8. doi: 10.1016/j.taap.2011.12.025.

Hughes, S. D., N. Ketheesan, and N. Haleagrahara. 2017. The therapeutic potential of plant flavonoids on rheumatoid arthritis. *Critical Reviews in Food Science and Nutrition* 57 (17):3601–13. doi: 10.1080/10408398.2016.1246413.

Hwang, J.-K., E.-M. Noh, S.-J. Moon, J.-M. Kim, K.-B. Kwon, B.-H. Park, Y.-O. You, B.-M. Hwang, H.-J. Kim, B.-S. Kim, et al. 2013. Emodin suppresses inflammatory responses and joint destruction in collagen-induced arthritic mice. *Rheumatology (Oxford, England)* 52 (9):1583–91. doi: 10.1093/rheumatology/ket178.

Jackson, J. K., T. Higo, W. L. Hunter, and H. M. Burt. 2006. The antioxidants curcumin and quercetin inhibit inflammatory processes associated with arthritis. *Inflammation Research: Official Journal of the European Histamine Research Society* 55 (4):168–75. doi: 10.1007/s00011-006-0067-z.

Javadi, F., A. Ahmadzadeh, S. Eghtesadi, N. Aryaeian, M. Zabihiyeganeh, A. R. Foroushani, and S. Jazayeri. 2017. The effect of quercetin on inflammatory factors and clinical symptoms in women with rheumatoid arthritis: A double-blind, randomized controlled trial. *Journal of the American College of Nutrition* 36 (1):9–15. doi: 10.1080/07315724.2016.1140093.

Javadi, F., S. Eghtesadi, A. Ahmadzadeh, N. Aryaeian, M. Zabihiyeganeh, A. R. Foroushani, and S. Jazayeri. 2014. The effect of quercetin on plasma oxidative status, C-reactive protein and blood pressure in women with rheumatoid arthritis. *International Journal of Preventive Medicine* 5 (3):293–301.

Ji, G., Y. Zhang, Q. Yang, S. Cheng, J. Hao, X. Zhao, and Z. Jiang. 2012. Genistein suppresses LPS-induced inflammatory response through inhibiting NF-κB following AMP kinase activation in RAW 264.7 macrophages. *PLoS One* 7 (12):e53101. doi: 10.1371/journal.pone.0053101.

Joskova, M., V. Sadlonova, G. Nosalova, E. Novakova, and S. Franova. 2013. Polyphenols and their components in experimental allergic asthma. In *Respiratory regulation-The molecular approach*, 91–8. Dordrecht: Springer.

Juurlink, B. H., H. J. Azouz, A. M. Aldalati, B. M. AlTinawi, and P. Ganguly. 2014. Hydroxybenzoic acid isomers and the cardiovascular system. *Nutrition Journal* 13 (1):63. doi: 10.1186/1475-2891-13-63.

Kakkar, M., T. Behl, P. Nijhawan, M. Grover, D. Jaglan, R. K. Pandey, and K. R. Binjam. 2020. Exploration of combined effect of peroxisome proliferator activated receptor (PPAR) agonist and retinoic acid receptor (RAR) agonist on experimental models of inflammation in rats. *Obesity Medicine* 19 (September 2020):100260.

Khan, H., A. Sureda, T. Belwal, S. Çetinkaya, İ. Süntar, S. Tejada, H. Devkota, H. Ullah, and M. Aschner. 2019. Polyphenols in the treatment of autoimmune diseases. *Autoimmunity Reviews* 18 (7):647–57. doi: 10.1016/j.autrev.2019.05.001.

Khojah, H. M., S. Ahmed, M. S. Abdel-Rahman, and E. H. Elhakeim. 2018. Resveratrol as an effective adjuvant therapy in the

management of rheumatoid arthritis: A clinical study. *Clinical Rheumatology* 37 (8):2035–42. doi: 10.1007/s10067-018-4080-8.

Khurana, R., and S. M. Berney. 2005. Clinical aspects of rheumatoid arthritis. *Pathophysiology: The Official Journal of the International Society for Pathophysiology* 12 (3):153–65. doi: 10.1016/j.pathophys.2005.07.009.

Kihara, M., R. Davies, L. Kearsley-Fleet, K. D. Watson, M. Lunt, D. P. M. Symmons, K. L. Hyrich, and British Society for Rheumatology Biologics Register. 2017. Use and effectiveness of tocilizumab among patients with rheumatoid arthritis: An observational study from the British Society for Rheumatology Biologics Register for rheumatoid arthritis. *Clinical Rheumatology* 36 (2):241–50. doi: 10.1007/s10067-016-3485-5.

Kim, E. K., and E. J. Choi. 2010. Pathological roles of MAPK signaling pathways in human diseases. *Biochimica et Biophysica Acta (Bba) - Molecular Basis of Disease* 1802 (4):396–405. doi: 10.1016/j.bbadis.2009.12.009.

Kim, E. Y., and K. D. Moudgil. 2017. Immunomodulation of autoimmune arthritis by pro-inflammatory cytokines. *Cytokine* 98:87–96. doi: 10.1016/j.cyto.2017.04.012.

Kim, H. P., K. H. Son, H. W. Chang, and S. S. Kang. 2004. Anti-inflammatory plant flavonoids and cellular action mechanisms. *Journal of Pharmacological Sciences* 96 (3):0411110005.

Kim, J.-E., J. E. Son, S. K. Jung, N. J. Kang, C. Y. Lee, K. W. Lee, and H. J. Lee. 2010. Cocoa polyphenols 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. *British Journal of Nutrition* 104 (7):957–64. doi: 10.1017/S0007114510001704.

Kim, K., T. M. Vance, and O. K. Chun. 2016. Greater flavonoid intake is associated with improved CVD risk factors in US adults. *British Journal of Nutrition* 115 (8):1481–1488. doi: 10.1017/S0007114516000519.

Kim, S. W., C. E. Kim, and M. H. Kim. 2011. Flavonoids inhibit high glucose-induced up-regulation of ICAM-1 via the p38 MAPK pathway in human vein endothelial cells. *Biochemical and Biophysical Research Communications* 415 (4):602–607. doi: 10.1016/j.bbrc.2011.10.115.

Kloesch, B., T. Becker, E. Dietersdorfer, H. Kiener, and G. Steiner. 2013. Anti-inflammatory and apoptotic effects of the polyphenol curcumin on human fibroblast-like synoviocytes. *International Immunopharmacology* 15 (2):400–405. doi: 10.1016/j.intimp.2013.01.003.

Kometani, T., T. Fukuda, T. Kakuma, K. Kawaguchi, W. Tamura, Y. Kumazawa, and K. Nagata. 2008. Effects of alpha-glucosylhesperidin, a bioactive food material, on collagen-induced arthritis in mice and rheumatoid arthritis in humans. *Immunopharmacology and Immunotoxicology* 30 (1):117–134. doi: 10.1080/08923970701812688.

Kronski, E., M. E. Fiori, O. Barbieri, S. Astigiano, V. Mirisola, P. H. Killian, A. Bruno, A. Pagani, F. Rovera, U. Pfeffer, et al. 2014. miR181b is induced by the chemopreventive polyphenol curcumin and inhibits breast cancer metastasis via down-regulation of the inflammatory cytokines CXCL1 and -2. *Molecular Oncology* 8 (3):581–595. doi: 10.1016/j.molonc.2014.01.005.

Kumar, P., B. Paul, S. Kumar, M. Ali, and A. K. Sexana. 2004. Correlation of cytokines and mobility in mice with arthritis and during therapy with Swertia chirayita. *Journal of Herbal Pharmacotherapy* 4 (2):33–45.

Kwak, S. C., C. Lee, J. Y. Kim, H. M. Oh, H. S. So, M. S. Lee, M. C. Rho, and J. Oh. 2013. Chlorogenic acid inhibits of osteoclast differentiation and bone resorption by down-regulation of receptor activator of nuclear factor kappa-b ligand-induced nuclear factor of activated T cells c1 expression. *Biological and Pharmaceutical Bulletin* 36 (11):b13-00430.

Lättig, J., M. Böhl, P. Fischer, S. Tischer, C. Tietböhl, M. Menschikowski, H. O. Gutzeit, P. Metz, and M. T. Pisabarro. 2007. Mechanism of inhibition of human secretory phospholipase A2 by flavonoids: Rationale for lead design. *Journal of Computer-Aided Molecular Design* 21 (8):473–483. doi: 10.1007/s10822-007-9129-8.

Lee, J.-D., J.-E. Huh, G. Jeon, H.-R. Yang, H.-S. Woo, D.-Y. Choi, and D.-S. Park. 2009. Flavonol-rich RVHxR from Rhus verniciflua Stokes and its major compound fisetin inhibits inflammation-related cytokines and angiogenic factor in rheumatoid arthritic fibroblast-like synovial cells and in vivo models. *International Immunopharmacology* 9 (3):268–276. doi: 10.1016/j.intimp.2008.11.005.

Lee, S. H., H.-H. Park, J.-E. Kim, J.-A. Kim, Y. H. Kim, C.-D. Jun, and S.-H. Kim. 2007. Allose gallates suppress expression of pro-inflammatory cytokines through attenuation of NF-kappaB in human mast cells. *Planta Medica* 73 (8):769–773. doi: 10.1055/s-2007-981553.

Lee, S.-Y., Y. O. Jung, J.-G. Ryu, H.-J. Oh, H.-J. Son, S. H. Lee, J.-E. Kwon, E.-K. Kim, M.-K. Park, S.-H. Park, et al. 2016. Epigallocatechin-3-gallate ameliorates autoimmune arthritis by reciprocal regulation of T helper-17 regulatory T cells and inhibition of osteoclastogenesis by inhibiting STAT3 signaling. *Journal of Leukocyte Biology* 100 (3):559–568. doi: 10.1189/jlb.3A0514-261RR.

Leichsenring, A., I. Bäcker, P. G. Furtmüller, C. Obinger, F. Lange, and J. Flemmig. 2016. Long-term effects of (-)-epigallocatechin gallate (EGCG) on pristane-induced arthritis (PIA) in female dark agouti rats. *PLoS One* 11 (3):e0152518. doi: 10.1371/journal.pone.0152518.

Li, A. N., S. Li, Y. J. Zhang, X. R. Xu, Y. M. Chen, and H. B. Li. 2014. Resources and biological activities of natural polyphenols. *Nutrients* 6 (12):6020–6047. doi: 10.3390/nu6126020.

Li, H., Z. Jia, A. Li, G. Jenkins, X. Yang, J. Hu, and W. Guo. 2013. Resveratrol repressed viability of U251 cells by miR-21 inhibiting of NF-κB pathway. *Molecular and Cellular Biochemistry* 382 (1-2):137–143. doi: 10.1007/s11010-013-1728-1.

Li, J., H. C. Hsu, and a J. D. Mountz. 2012. Managing macrophages in rheumatoid arthritis by reform or removal. *Current Rheumatology Reports* 14 (5):445–454. doi: 10.1007/s11926-012-0272-4.

Li, J., J. Li, Y. Yue, Y. Hu, W. Cheng, R. Liu, X. Pan, and P. Zhang. 2014. Genistein suppresses tumor necrosis factor α-induced inflammation via modulating reactive oxygen species/Akt/nuclear factor κB and adenosine monophosphate-activated protein kinase signal pathways in human synoviocyte MH7A cells. *Drug Design, Development and Therapy* 8:315–323. doi: 10.2147/DDDT.S52354.

Liu, T., L. Zhang, D. Joo, and S. C. Sun. 2017. NF-κB signaling in inflammation. *Signal Transduction and Targeted Therapy* 2 (1):1–9. doi: 10.1038/sigtrans.2017.23.

Liu, W., and J. Li. 2019. Theaflavin-3, 3'-digallate attenuates rheumatoid inflammation in mice through the nuclear factor-κB and MAPK pathways. *Archivum Immunologiae et Therapiae Experimentalis* 67 (3):153–160. doi: 10.1007/s00005-019-00536-7.

Liu, X.-Y., L. Xu, Y. Wang, J.-X. Li, Y. Zhang, C. Zhang, S.-S. Wang, and X.-M. Zhang. 2017. Protective effects of total flavonoids of Astragalus against adjuvant-induced arthritis in rats by regulating OPG/RANKL/NF-κB pathway. *International Immunopharmacology* 44:105–114. doi: 10.1016/j.intimp.2017.01.010.

Liu, Z., C. Jiang, J. Zhang, B. Liu, and Q. Du. 2016. Resveratrol inhibits inflammation and ameliorates insulin resistant endothelial dysfunction via regulation of AMP-activated protein kinase and sirtuin 1 activities. *Journal of Diabetes* 8 (3):324–335. doi: 10.1111/1753-0407.12296.

Lou, Z., X. Li, X. Zhao, K. Du, X. Li, and B. Wang. 2018. Resveratrol attenuates hydrogen peroxide-induced apoptosis, reactive oxygen species generation, and PSGL-1 and VWF activation in human umbilical vein endothelial cells, potentially via MAPK signalling pathways. *Molecular Medicine Reports* 17 (2):2479–2487.

Luczkiewicz, P., A. Kokotkiewicz, A. Dampc, and M. Luczkiewicz. 2014. Mangiferin: A promising therapeutic agent for rheumatoid arthritis treatment. *Medical Hypotheses* 83 (5):570–574. doi: 10.1016/j.mehy.2014.08.021.

Magrone, T., M. Magrone, M. A. Russo, and E. Jirillo. 2019. Recent advances on the anti-inflammatory and antioxidant properties of red grape polyphenols: In vitro and in vivo studies. *Antioxidants* 9 (1):35. doi: 10.3390/antiox9010035.

Malireddy, S., S. R. Kotha, J. D. Secor, T. O. Gurney, J. L. Abbott, G. Maulik, K. R. Maddipati, and N. L. Parinandi. 2012. Phytochemical antioxidants modulate mammalian cellular epigenome: Implications

in health and disease. *Antioxidants & Redox Signaling* 17 (2): 327–339. doi: 10.1089/ars.2012.4600.

Manach, C., A. Scalbert, C. Morand, C. Rémésy, and L. Jiménez. 2004. Polyphenols: Food sources and bioavailability. *The American Journal of Clinical Nutrition* 79 (5):727–747. doi: 10.1093/ajcn/79.5.727.

Mateen, S., S. Moin, A. Zafar, and A. Q. Khan. 2016. Redox signaling in rheumatoid arthritis and the preventive role of polyphenols. *Clinica Chimica Acta* 463:4–10. doi: 10.1016/j.cca.2016.10.007.

Maugeri, A., M. Barchitta, M. Mazzone, F. Giuliano, G. Basile, and A. Agodi. 2018. Resveratrol modulates SIRT1 and DNMT functions and restores LINE-1 methylation levels in ARPE-19 cells under oxidative stress and inflammation. *International Journal of Molecular Sciences* 19 (7):2118. doi: 10.3390/ijms19072118.

McInnes, I. B., and G. Schett. 2011. The pathogenesis of rheumatoid arthritis. *New England Journal of Medicine* 365 (23):2205–2219. doi: 10.1056/NEJMra1004965.

Min, S.-Y., M. Yan, S. B. Kim, S. Ravikumar, S.-R. Kwon, K. Vanarsa, H.-Y. Kim, L. S. Davis, and C. Mohan. 2015. Green tea epigallocatechin-3-gallate suppresses autoimmune arthritis through indoleamine-2, 3-dioxygenase expressing dendritic cells and the nuclear factor, erythroid 2-like 2 antioxidant pathway. *Journal of Inflammation* 12 (1):1–15. doi: 10.1186/s12950-015-0097-9.

Mokni, M., F. Limam, S. Elkahoui, M. Amri, and E. Aouani. 2007. Strong cardioprotective effect of resveratrol, a red wine polyphenol, on isolated rat hearts after ischemia/reperfusion injury. *Archives of Biochemistry and Biophysics* 457 (1):1–6. doi: 10.1016/j.abb.2006.10.015.

Morinobu, A., W. Biao, S. Tanaka, M. Horiuchi, L. Jun, G. Tsuji, Y. Sakai, M. Kurosaka, and S. Kumagai. 2008. (−)-Epigallocatechin-3-gallate suppresses osteoclast differentiation and ameliorates experimental arthritis in mice. *Arthritis & Rheumatism* 58 (7):2012–2018. doi: 10.1002/art.23594.

Naczk, M., and F. Shahidi. 2006. Phenolics in cereals, fruits and vegetables: Occurrence, extraction and analysis. *Journal of Pharmaceutical and Biomedical Analysis* 41 (5):1523–1542. doi: 10.1016/j.jpba.2006.04.002.

Nam, N. H. 2006. Naturally occurring NF-kappaB inhibitors. *Mini Reviews in Medicinal Chemistry* 6 (8):945–951. doi: 10.2174/138955706777934937.

Nandi, P., G. H. Kingsley, and D. L. Scott. 2008. Disease-modifying antirheumatic drugs other than methotrexate in rheumatoid arthritis and seronegative arthritis. *Current Opinion in Rheumatology* 20 (3): 251–256. doi: 10.1097/BOR.0b013e3282fb7caa.

Neog, M. K., S. Joshua Pragasam, M. Krishnan, and M. Rasool. 2017. p-Coumaric acid, a dietary polyphenol ameliorates inflammation and curtails cartilage and bone erosion in the rheumatoid arthritis rat model. *BioFactors (Oxford, England)* 43 (5):698–717. doi: 10.1002/biof.1377.

Nijhawan, P., and T. Behl. 2020a. Role of endostatin in rheumatoid arthritis. *Current Rheumatology Reviews* 17 (1):68–75.

Nijhawan, P., and T. Behl. 2020b. Nutraceuticals in the management of obesity. *Obesity Medicine* 17:100168. doi: 10.1016/j.obmed.2019.100168.

Oka, Y., S. Iwai, H. Amano, et al. 2011. Tea polyphenols inhibit rat osteoclast formation and differentiation. *Journal of Pharmacological Sciences* 118 (1):1112190632.

Oliveira, A., V. Monteiro, K. Navegantes-Lima, J. Reis, R. Gomes, D. Rodrigues, S. Gaspar, and M. Monteiro. 2017. Resveratrol role in autoimmune disease—A mini-review. *Nutrients* 9 (12):1306. doi: 10.3390/nu9121306.

Oliviero, F., A. Scanu, Y. Zamudio-Cuevas, L. Punzi, and P. Spinella. 2018. Anti-inflammatory effects of polyphenols in arthritis. *Journal of the Science of Food and Agriculture* 98 (5):1653–1659. doi: 10.1002/jsfa.8664.

Pandey, K. B., and S. I. Rizvi. 2009. Plant polyphenols as dietary antioxidants in human health and disease. *Oxidative Medicine and Cellular Longevity* 2 (5):270–278. doi: 10.4161/oxim.2.5.9498.

Park, C., D.-O. Moon, I.-W. Choi, B. T. Choi, T.-J. Nam, C.-H. Rhu, T. K. Kwon, W. H. Lee, G.-Y. Kim, Y. H. Choi, et al. 2007. Curcumin induces apoptosis and inhibits prostaglandin E2 production in synovial fibroblasts of patients with rheumatoid arthritis. *International Journal of Molecular Medicine* 20 (3):365–372.

Pašková, Ľ., V., Kuncirova, S. Poništ, D. Mihálová, R. Nosál, J. Harmatha, I. Hrádková, T. Čavojský, F. Bilka, K. Šišková, et al. 2016. Effect of N-feruloylserotonin and methotrexate on severity of experimental arthritis and on messenger RNA expression of key proinflammatory markers in liver. *Journal of Immunology Research* 2016:1–12.

Petti, S., and C. Scully. 2009. Polyphenols, oral health and disease: A review. *Journal of Dentistry* 37 (6):413–423. doi: 10.1016/j.jdent.2009.02.003.

Pragasam, S. J., V. Venkatesan, and M. Rasool. 2013. Immunomodulatory and anti-inflammatory effect of p-coumaric acid, a common dietary polyphenol on experimental inflammation in rats. *Inflammation* 36 (1):169–176. doi: 10.1007/s10753-012-9532-8.

Rahman, I., and S. Chung. 2010. Dietary polyphenols, deacetylases and chromatin remodeling in inflammation. *Personalized Nutrition* 101: 84–94.

Ramadan, G., M. A. Al-Kahtani, and W. M. El-Sayed. 2011. Anti-inflammatory and anti-oxidant properties of Curcuma longa (turmeric) versus Zingiber officinale (ginger) rhizomes in rat adjuvant-induced arthritis. *Inflammation* 34 (4):291–301. doi: 10.1007/s10753-010-9278-0.

Rathi, B., S. Bodhankar, V. Mohan, and P. Thakurdesai. 2013. Ameliorative effects of a polyphenolic fraction of Cinnamomum zeylanicum L. bark in animal models of inflammation and arthritis. *Scientia Pharmaceutica* 81 (2):567–590. doi: 10.3797/scipharm.1301-16.

Rengasamy, K. R. R., H. Khan, S. Gowrishankar, R. J. L. Lagoa, F. M. Mahomoodally, Z. Khan, S. Suroowan, D. Tewari, G. Zengin, S. T. S. Hassan, et al. 2019. The role of flavonoids in autoimmune diseases: Therapeutic updates. *Pharmacology & Therapeutics* 194: 107–131. doi: 10.1016/j.pharmthera.2018.09.009.

Rosillo, M. Á., M. J. Alcaraz, M. Sánchez-Hidalgo, J. G. Fernández-Bolaños, C. Alarcón-de-la-Lastra, and M. L. Ferrándiz. 2014. Anti-inflammatory and joint protective effects of extra-virgin olive-oil polyphenol extract in experimental arthritis. *The Journal of Nutritional Biochemistry* 25 (12):1275–1281. doi: 10.1016/j.jnutbio.2014.07.006.

Rosillo, M. A., M. Sánchez-Hidalgo, A. González-Benjumea, J. G. Fernández-Bolaños, E. Lubberts, and C. Alarcón-de-la-Lastra. 2015. Preventive effects of dietary hydroxytyrosol acetate, an extra virgin olive oil polyphenol in murine collagen-induced arthritis. *Molecular Nutrition & Food Research* 59 (12):2537–2546. doi: 10.1002/mnfr.201500304.

Roubille, C., V. Richer, T. Starnino, C. McCourt, A. McFarlane, P. Fleming, S. Siu, J. Kraft, C. Lynde, J. Pope, et al. 2015. The effects of tumour necrosis factor inhibitors, methotrexate, non-steroidal anti-inflammatory drugs and corticosteroids on cardiovascular events in rheumatoid arthritis, psoriasis and psoriatic arthritis: A systematic review and meta-analysis. *Annals of the Rheumatic Diseases* 74 (3): 480–489. doi: 10.1136/annrheumdis-2014-206624.

Santangelo, C., R. Varì, B. Scazzocchio, R. D. Benedetto, C. Filesi, and R. Masella. 2007. Polyphenols, intracellular signalling and inflammation. *Annali Dell'Istituto Superiore di Sanita* 43 (4):394–405.

Sena, L. A., and N. S. Chandel. 2012. Physiological roles of mitochondrial reactive oxygen species. *Molecular Cell* 48 (2):158–167. doi: 10.1016/j.molcel.2012.09.025.

Serafini, M., I. Peluso, and A. Raguzzini. 2010. Flavonoids as anti-inflammatory agents. *Proceedings of the Nutrition Society* 69 (3): 273–278. doi: 10.1017/S002966511000162X.

Seven, A., S. Güzel, M. Aslan, and V. Hamuryudan. 2008. Lipid, protein, DNA oxidation and antioxidant status in rheumatoid arthritis. *Clinical Biochemistry* 41 (7-8):538–543. doi: 10.1016/j.clinbiochem.2008.01.029.

Sevgi, K., B. Tepe, and C. Sarikurkcu. 2015. Antioxidant and DNA damage protection potentials of selected phenolic acids. *Food and Chemical Toxicology: An International Journal Published for the*

British Industrial Biological Research Association 77:12–21. doi: 10.1016/j.fct.2014.12.006.

Shukla, P. K., L. Gautam, M. Sinha, P. Kaur, S. Sharma, and T. P. Singh. 2015. Structures and binding studies of the complexes of phospholipase A2 with five inhibitors. *Biochimica et Biophysica Acta (Bba) - Proteins and Proteomics* 1854 (4):269–277. doi: 10.1016/j.bbapap.2014.12.017.

Simon, E., P. Aswini, V. B. Sameer Kumar, and G. Mankadath. 2018. Curcumin and its synthetic analogue dimethoxycurcumin differentially modulates antioxidant status of normal human peripheral blood mononuclear cells. *Free Radical Research* 52 (5):583–591. doi: 10.1080/10715762.2018.1455002.

Singh, J. A., A. Hossain, A. S. Mudano, E. T. Ghogomu, M. E. Suarez-Almazor, R. Buchbinder, L. J. Maxwell, P. Tugwell, and G. A. Wells. 2017. Biologics or tofacitinib for people with rheumatoid arthritis naive to methotrexate: A systematic review and network meta-analysis. *Cochrane Database of Systematic Reviews* 5 (5):1–161.

Sirerol, J. A., M. L. Rodríguez, S. Mena, M. A. Asensi, J. M. Estrela, and A. L. Ortega. 2016. Role of natural stilbenes in the prevention of cancer. *Oxidative Medicine and Cellular Longevity* 2016:1–15. doi: 10.1155/2016/3128951.

Steinmann, J., J. Buer, T. Pietschmann, and E. Steinmann. 2013. Anti-infective properties of epigallocatechin-3-gallate (EGCG), a component of green tea. *British Journal of Pharmacology* 168 (5): 1059–1073. doi: 10.1111/bph.12009.

Sultana, F., M. K. Neog, and M. Rasool. 2017. Targeted delivery of morin, a dietary bioflavanol encapsulated mannosylated liposomes to the macrophages of adjuvant-induced arthritis rats inhibits inflammatory immune response and osteoclastogenesis. *European Journal of Pharmaceutics and Biopharmaceutics: Official Journal of Arbeitsgemeinschaft Fur Pharmazeutische Verfahrenstechnik e.V* 115: 229–242. doi: 10.1016/j.ejpb.2017.03.009.

Sun, H. Z., T. W. Yang, W. J. Zang, and S. F. Wu. 2010. Dehydroepiandrosterone-induced proliferation of prostatic epithelial cell is mediated by NFKB via PI3K/AKT signaling pathway. *Journal of Endocrinology* 204 (3):311–318. doi: 10.1677/JOE-09-0270.

Sung, S., D. Kwon, E. Um, and B. Kim. 2019. Could polyphenols help in the control of rheumatoid arthritis? *Molecules* 24 (8):1589.

Tanaka, T., M. Narazaki, and T. Kishimoto. 2018. Interleukin (IL-6) immunotherapy. *Cold Spring Harbor Perspectives in Biology* 10 (8): a028456. doi: 10.1101/cshperspect.a028456.

Tanaka, T., A. Ogata, and M. Narazaki. 2013. Tocilizumab: An updated review of its use in the treatment of rheumatoid arthritis and its application for other immune-mediated diseases. *Clinical Medicine Insights: Therapeutics* 5:CMT-S9282.

Tang, L. L., J. S. Gao, X. R. Chen, and X. Xie. 2006. Inhibitory effect of resveratrol on the proliferation of synoviocytes in rheumatoid arthritis and its mechanism in vitro. *Zhong nan da xue xue bao. Yi xue ban = Journal of Central South University. Medical Sciences* 31 (4): 528.

Tekeoglu, I., A. Dogan, L. Ediz, M. Budancamanak, and A. Demirel. 2007. Effects of thymoquinone (volatile oil of black cumin) on rheumatoid arthritis in rat models. *Phytotherapy Research* 21 (9): 895–897. doi: 10.1002/ptr.2143.

Tian, J., J. W. Chen, J. S. Gao, L. Li, and X. Xie. 2013. Resveratrol inhibits TNF-α-induced IL-1β, MMP-3 production in human rheumatoid arthritis fibroblast-like synoviocytes via modulation of PI3kinase/Akt pathway. *Rheumatology International* 33 (7): 1829–1835. doi: 10.1007/s00296-012-2657-0.

Tsai, M.-H., L.-F. Hsu, C.-W. Lee, Y.-C. Chiang, M.-H. Lee, J.-M. How, C.-M. Wu, C.-L. Huang, and I.-T. Lee. 2017. Resveratrol inhibits urban particulate matter-induced COX-2/PGE2 release in human fibroblast-like synoviocytes via the inhibition of activation of NADPH oxidase/ROS/NF-κB. *The International Journal of Biochemistry & Cell Biology* 88:113–123. doi: 10.1016/j.biocel.2017.05.015.

Tsubaki, M., T. Takeda, T. Kino, T. Itoh, M. Imano, G. Tanabe, O. Muraoka, T. Satou, and S. Nishida. 2015. Mangiferin suppresses CIA by suppressing the expression of TNF-α, IL-6, IL-1β, and RANKL through inhibiting the activation of NF-κB and ERK1/2. *American Journal of Translational Research* 7 (8):1371–1381.

Ullah, H., and H. Khan. 2018. Anti-Parkinson potential of silymarin: Mechanistic insight and therapeutic standing. *Frontiers in Pharmacology* 9:422. doi: 10.3389/fphar.2018.00422.

Umar, S., O. Hedaya, A. K. Singh, and S. Ahmed. 2015. Thymoquinone inhibits TNF-α-induced inflammation and cell adhesion in rheumatoid arthritis synovial fibroblasts by ASK1 regulation. *Toxicology and Applied Pharmacology* 287 (3):299–305. doi: 10.1016/j.taap.2015.06.017.

Umar, S., A. Kumar, M. Sajad, J. Zargan, M. Ansari, S. Ahmad, C. K. Katiyar, and H. A. Khan. 2013. Hesperidin inhibits collagen-induced arthritis possibly through suppression of free radical load and reduction in neutrophil activation and infiltration. *Rheumatology International* 33 (3):657–663. doi: 10.1007/s00296-012-2430-4.

Umeno, A., M. Horie, K. Murotomi, Y. Nakajima, and Y. Yoshida. 2016. Antioxidative and antidiabetic effects of natural polyphenols and isoflavones. *Molecules* 21 (6):708. doi: 10.3390/molecules21060708.

Vaillancourt, F., P. Silva, Q. Shi, H. Fahmi, J. C. Fernandes, and M. Benderdour. 2011. Elucidation of molecular mechanisms underlying the protective effects of thymoquinone against rheumatoid arthritis. *Journal of Cellular Biochemistry* 112 (1):107–117. doi: 10.1002/jcb.22884.

Venkatachalam, K., S. Mummidi, D. M. Cortez, S. D. Prabhu, A. J. Valente, and B. Chandrasekar. 2008. Resveratrol inhibits high glucose-induced PI3K/Akt/ERK-dependent interleukin-17 expression in primary mouse cardiac fibroblasts. *American Journal of Physiology. Heart and Circulatory Physiology* 294 (5):H2078–H2087. doi: 10.1152/ajpheart.01363.2007.

Vetal, S., S. L. Bodhankar, V. Mohan, and P. A. Thakurdesai. 2013. Anti-inflammatory and anti-arthritic activity of type-A procyanidine polyphenols from bark of Cinnamomum zeylanicum in rats. *Food Science and Human Wellness* 2 (2):59–67. doi: 10.1016/j.fshw.2013.03.003.

Viatte, S., D. Plant, and S. Raychaudhuri. 2013. Genetics and epigenetics of rheumatoid arthritis. *Nature Reviews. Rheumatology* 9 (3): 141–153. doi: 10.1038/nrrheum.2012.237.

Vos, T., C. Allen, M. Arora, R. M. Barber, Z. A. Bhutta, A. Brown, A. Carter, D. C. Casey, F. J. Charlson, A. Z. Chen, et al. 2016. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: A systematic analysis for the Global Burden of Disease Study 2015. *The Lancet* 388 (10053):1545–1602. doi: 10.1016/S0140-6736(16)31678-6.

Wada, T., T. Nakashima, N. Hiroshi, and J. M. Penninger. 2006. RANKL-RANK signaling in osteoclastogenesis and bone disease. *Trends in Molecular Medicine* 12 (1):17–25. doi: 10.1016/j.molmed.2005.11.007.

Wadsworth, T. L., T. L. McDonald, and D. R. Koop. 2001. Effects of Ginkgo biloba extract (EGb 761) and quercetin on lipopolysaccharide-induced signaling pathways involved in the release of tumor necrosis factor-alpha. *Biochemical Pharmacology* 62 (7):963–974. doi: 10.1016/s0006-2952(01)00734-1.

Wahba, M. G., B. A. Messiha, and A. A. Abo-Saif. 2016. Protective effects of fenofibrate and resveratrol in an aggressive model of rheumatoid arthritis in rats. *Pharmaceutical Biology* 54 (9): 1705–1715. doi: 10.3109/13880209.2015.1125931.

Wai Kan Yeung, A., B. B. Aggarwal, D. Barreca, et al. 2018. Dietary natural products and their potential to influence health and disease including animal model studies. *Animal Science Papers & Reports* 36 (4):345–358.

Wang, J., T. Wei, J. Gao, H. He, X. Chang, and T. Yan. 2015. Effects of Naringenin on inflammation in complete freund's adjuvant-induced arthritis by regulating Bax/Bcl-2 balance. *Inflammation* 38 (1):245–251.

Wang, J., Q. Zhang, S. Jin, D. He, S. Zhao, and S. Liu. 2008. Genistein modulate immune responses in collagen-induced rheumatoid arthritis model. *Maturitas* 59 (4):405–412. doi: 10.1016/j.maturitas.2008.04.003.

Wang, X., G. Fang, Y. Yang, and Y. Pang. 2019. The newly discovered natural compounds against rheumatoid arthritis-an overview. *Phytochemistry Letters* 34:50–58. doi: 10.1016/j.phytol.2019.09.011.

Wheeler, D. S., J. D. Catravas, K. Odoms, A. Denenberg, V. Malhotra, and H. R. Wong. 2004. Epigallocatechin-3-gallate, a green tea–derived polyphenol, inhibits IL-1β-dependent proinflammatory signal transduction in cultured respiratory epithelial cells. *The Journal of Nutrition* 134 (5):1039–1044. doi: 10.1093/jn/134.5.1039.

Wu, D., J. Wang, M. Pae, and S. N. Meydani. 2012. Green tea EGCG, T cells, and T cell-mediated autoimmune diseases. *Molecular Aspects of Medicine* 33 (1):107–118. doi: 10.1016/j.mam.2011.10.001.

Xuzhu, G., M. Komai-Koma, B. P. Leung, H. S. Howe, C. McSharry, I. B. McInnes, and D. Xu. 2012. Resveratrol modulates murine collagen-induced arthritis by inhibiting Th17 and B-cell function. *Annals of the Rheumatic Diseases* 71 (1):129–135. doi: 10.1136/ard.2011.149831.

Yahfoufi, N., N. Alsadi, M. Jambi, and C. Matar. 2018. The immunomodulatory and anti-inflammatory role of polyphenols. *Nutrients* 10 (11):1618. doi: 10.3390/nu10111618.

Yang, E.-J., J. Lee, S.-Y. Lee, E.-K. Kim, Y.-M. Moon, Y. O. Jung, S.-H. Park, and M.-L. Cho. 2014. EGCG attenuates autoimmune arthritis by inhibition of STAT3 and HIF-1α with Th17/Treg control. *PLoS One* 9 (2):e86062. doi: 10.1371/journal.pone.0086062.

Yang, G., C.-C. Chang, Y. Yang, L. Yuan, L. Xu, C.-T. Ho, and S. Li. 2018. Resveratrol alleviates rheumatoid arthritis via reducing ROS and inflammation, inhibiting MAPK signaling pathways, and suppressing angiogenesis. *Journal of Agricultural and Food Chemistry* 66 (49):12953–12960. doi: 10.1021/acs.jafc.8b05047.

Yeo, S. C. M., P. S. Fenwick, P. J. Barnes, H. S. Lin, and L. E. Donnelly. 2017. Isorhapontigenin, a bioavailable dietary polyphenol, suppresses airway epithelial cell inflammation through a corticosteroid-independent mechanism. *British Journal of Pharmacology* 174 (13):2043–2059. doi: 10.1111/bph.13803.

Yoon, H.-Y., E.-G. Lee, H. Lee, I. J. Cho, Y. J. Choi, M.-S. Sung, H.-G. Yoo, and W.-H. Yoo. 2013. Kaempferol inhibits IL-1β-induced proliferation of rheumatoid arthritis synovial fibroblasts and the production of COX-2, PGE2 and MMPs. *International Journal of Molecular Medicine* 32 (4):971–977. doi: 10.3892/ijmm.2013.1468.

Yoon, J. H., and S. J. Baek. 2005. Molecular targets of dietary polyphenols with anti-inflammatory properties. *Yonsei Medical Journal* 46 (5):585–596. doi: 10.3349/ymj.2005.46.5.585.

You, S., J. H. Koh, L. Leng, W. U. Kim, and R. Bucala. 2018. The tumor-like phenotype of rheumatoid synovium: Molecular profiling and prospects for precision medicine. *Arthritis & Rheumatology (Hoboken, N.J.)* 70 (5):637–652. doi: 10.1002/art.40406.

Yun, H. J., W. H. Yoo, M. K. Han, Y. R. Lee, J. S. Kim, and S. I. Lee. 2008. Epigallocatechin-3-gallate suppresses TNF-alpha -induced production of MMP-1 and -3 in rheumatoid arthritis synovial fibroblasts. *Rheumatology International* 29 (1):23–29. doi: 10.1007/s00296-008-0597-5.

Zamora-Ros, R., C. Andres-Lacueva, R. M. Lamuela-Raventós, T. Berenguer, P. Jakszyn, C. Martínez, M. J. Sánchez, C. Navarro, M. D. Chirlaque, M.-J. Tormo, et al. 2008. Concentrations of resveratrol and derivatives in foods and estimation of dietary intake in a Spanish population: European Prospective Investigation into Cancer and Nutrition (EPIC)-Spain cohort. *British Journal of Nutrition* 100 (1):188–196. doi: 10.1017/S0007114507882997.

Zhang, J., X. Song, W. Cao, J. Lu, X. Wang, G. Wang, Z. Wang, and X. Chen. 2016. Autophagy and mitochondrial dysfunction in adjuvant-arthritis rats treatment with resveratrol. *Scientific Reports* 6: 32928. doi: 10.1038/srep32928.

Zhang, Y., J. Dong, P. He, W. Li, Q. Zhang, N. Li, and T. Sun. 2012. Genistein inhibit cytokines or growth factor-induced proliferation and transformation phenotype in fibroblast-like synoviocytes of rheumatoid arthritis. *Inflammation* 35 (1):377–387. doi: 10.1007/s10753-011-9365-x.

Zhao, C., T. Sakaguchi, K. Fujita, H. Ito, N. Nishida, A. Nagatomo, Y. Tanaka-Azuma, and Y. Katakura. 2016. Pomegranate-derived polyphenols reduce reactive oxygen species production via SIRT3-mediated SOD2 activation. *Oxidative Medicine and Cellular Longevity* 2016:1–9. doi: 10.1155/2016/2927131.

Zhao, L., F. Cen, F. Tian, M.-J. Li, Q. Zhang, H.-Y. Shen, X.-C. Shen, M.-M. Zhou, and J. Du. 2017. Combination treatment with quercetin and resveratrol attenuates high fat diet-induced obesity and associated inflammation in rats via the AMPKα1/SIRT1 signaling pathway. *Experimental and Therapeutic Medicine* 14 (6):4942–5948.

Zheng, W., Z. Feng, S. You, H. Zhang, Z. Tao, Q. Wang, H. Chen, and Y. Wu. 2017. Fisetin inhibits IL-1β-induced inflammatory response in human osteoarthritis chondrocytes through activating SIRT1 and attenuates the progression of osteoarthritis in mice. *International Immunopharmacology* 45:135–147. doi: 10.1016/j.intimp.2017.02.009.

Zhu, X., K. Zeng, Y. Qiu, F. Yan, and C. Lin. 2013. Therapeutic effect of emodin on collagen-induced arthritis in mice. *Inflammation* 36 (6):1253–1259. doi: 10.1007/s10753-013-9663-6.