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## ROLE OF PHYTOCHEMICALS TREATMENTS IN MANAGING RHEUMATOID ARTHRITIS (REVIEW ARTICLE)

*Non-steroidal anti-inflammatory drugs are one of the symptomatic treatment options for rheumatoid arthritis (RA). However, these medications are known to have multiple adverse effects. Although biological medications target molecular pathways involved in the inflammatory process of RA, there is a lack of long-term safety data. This review aims to present the novel insights of recent studies investigating medicinal plants, phytochemicals and their pharmacological activities against RA. Punicalagin reduces release of LPS-induced nitric oxide, TNF-α, and IL-6 by suppressing NF-κB and MAPK signaling pathways that are responsible for apoptosis of chondrocytes. Anthocyanins decrease the number of Th17 cells and suppress Th17 cells differentiation in vivo and in vitro. Also, anthocyanins inhibit osteoclasts via downregulation of cytokines including IL-1, IL-6, IL-17, and TNF-α in vitro. Oral ellagic acid in arthritic rats considerably decreases paw edema and levels of chitinase-3-like protein-1, which is induced via the NF-κB pathway and overexpression of which is associated with the inflammatory process of RA in chondrocytes and synovial tissue. Punicic acid reduces MMP9 gene expression, associated with the activation of NF-κB, which may mediate its anti-inflammatory effect in osteoarthritis. Although to date natural products are mainly used as nutraceuticals, the treatment of RA by medicinal plants needs more investigation to fully explore their potential as pharmacological agents in the treatment of autoimmune inflammatory diseases.*

***Key words:** rheumatoid arthritis, punicalagin, anthocyanins, ellagic acid, punicic acid, anti-inflammatory phytochemicals.*

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## РОЛЬ ФІТОЗАСОБІВ У ТЕРАПІЇ РЕВМАТОЇДНОГО АРТРИТУ (ОГЛЯДОВА СТАТТЯ)

*Нестероїдні протизапальні препарати є одним із варіантів симптоматичного лікування ревматоїдного артриту (РА). Однак відомо, що вони мають численні побічні ефекти. Незважаючи на те, що біологічні препарати спрямовані на молекулярні шляхи запалення, бракує даних про довгострокову безпеку щодо РА. Цей огляд має на меті представити нові ідеї останніх досліджень лікарських рослин, фітохімічних речовин та їх фармакологічні ефекти щодо РА. Пунікалагін зменшує вивільнення LPS-індукованого оксиду азоту, TNF-α та IL-6 шляхом пригнічення сигнальних шляхів NF-κB і MAPK, які відповідають за апоптоз хондроцитів. Антоціани зменшують кількість клітин Th17 і пригнічують диференціацію клітин Th17 in vivo та in vitro. Крім того, антоціани інгібують остеокласти шляхом зниження регуляції цитокінів, включаючи IL-1, IL-6, IL-17 і TNF-α in vitro. Елагова кислота у щурів з артритом значно зменшує набряк лапи та рівні хітинази-3-подібного білка-1, який індукується через шлях NF-κB і надмірна експресія якого пов'язана із запальним процесом у хондроцитах і синовіальній тканині. Пунікова кислота знижує експресію гена MMP9, пов'язану з активацією NF-κB, що може опосередковувати її протизапальну дію у разі остеоартриту. Хоча на сьогодні природні сполуки в основному використовуються як нутрицевтики, терапія РА лікарськими рослинами потребує додаткових досліджень, щоб повністю вивчити їхній потенціал як фармакологічних засобів у лікуванні аутоімунних запальних захворювань.*

***Ключові слова:** ревматоїдний артрит, пунікалагін, антоціани, елагова кислота, пунікова кислота, протизапальні фітохімічні речовини.*

**Introduction.** Rheumatoid arthritis (RA) is a chronic systemic inflammatory and autoimmune disease that essentially affects the joints. Although the severity of RA has reduced during recent decades, the disease prevalence has risen. According to population-based studies, the global prevalence of RA between 1980 and 2019 was 460 per 100.000 population. Trend analysis showed that RA was observed more in developed countries than developing countries (Finckh et al., 2022, pp. 591–602; Almutairi, 2020, pp. 863–877). This disease arises more in adult populations and is characterized by swelling, redness, pain and stiffness and progressive disability, affecting multiple joints symmetrically (Kaloni, Chakraborty, & Biswas, 2020, pp. 179–190). The role of several auto antibodies such as rheumatoid factor (RF), anti-citrullinated protein antibodies (ACPA) and anti-carbamylated protein antibodies (anti-CarP) in the pathogenesis of RA is evident. In synovial joints, type 1 T helper cells (Th1) are involved in the activation of macrophages that induce the production of pro-inflammatory cytokine like tumor necrosis factor (TNF) (Mueller et al., 2021, p. 3017). Although recent research has shown that interleukin (IL)-24 possesses anti-inflammatory effects, it (together with IL-20) was detected to be enhanced in plasma from patients with RA (Zhong, Zhang, & Chong, 2022, p. 627). Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the symptomatic treatment options for RA. However, these medications are known to have multiple adverse effects including nephrotoxicity, gastrointestinal bleeding and ulceration, increasing blood pressure and the risk of first hospitalization due to congestive heart failure. In order to control these reactions it is recommended to administer NSAIDs for a short period of time and in the lowest effective dose (Wongrakpanich, Wongrakpanich, & Melhado, 2018, pp. 143–150). Conventional disease modifying anti-rheumatic drugs (DMARDs) are usually the first choice to diminish disability and improve long-term outcomes for people with RA. Biologics are much more costly than other subsets of DMARDs, they are commonly used as partial responders to traditional DMARDs. Although the combination of biologics and traditional DMARDs has demonstrated improved efficacy, the potential benefits and harms (such as cancer and infections) are still controversial (Singh et al., 2016, p. CD012183). Various treatment strategies aim to suppress the activity of the disease. The introduction of synthetic and biologic DMARDs in very early stages of RA minimizes joint damage and functional disability, optimizing outcomes for patients. However, in spite of applying aggressive pharmacologic treatment regimens early in disease onset, complete clinical remission is not achieved (Guo et al., 2018, p. 15). Although biological medications seem to effectively target molecular pathways involved in the inflammatory process of RA, there is a lack of long-term safety data regarding their use. Moreover, biologic drugs appear to have some disadvantages. Among these is their chemical and physical volatility. Immunobiologicals should be stored, distributed and transported at specific temperatures (2–8°C) in order to avoid compromising their safety and efficacy. Patients need to be informed about home storage temperature condition monitoring via instructions provided by drug manufacturers (de Assis Damasceno et al., 2020, pp. 1–6). Various investigations have demonstrated an increased prevalence in the use of herbal medicine in developing countries. Since ancient times, herbs have been utilized as medicines for treating numerous diseases including inflammatory diseases. Interestingly, a rise in the prevalence of herbs used as complementary and alternative medicine among chronic disease patients has been reported in recent years (Peltzer & Pengpid, 2019, pp. 573–582; Welz, Emberger-Klein, & Menrad, 2018, p. 92). The anti-inflammatory properties of some herbal products are well-known and they have fewer unwanted effects than existing anti-inflammatory medications. As such, herbs and their derivatives constitute a promising arena in novel medical therapies. Furthermore, the cost-effectiveness of natural products has been explored and summarized by high quality studies (Xiong et al., 2022, p. 765226).

This article aims to present a review of novel insights into the use of medicinal plants, phytochemicals and their pharmacological activities against RA that have already been investigated via recent *in vivo*, *in vitro* experiments and clinical trials.

**Anti-inflammatory phytochemicals and their mechanism of actions.** Inflammation is a pathological process characterized by the accumulation of pro-inflammatory mediators at the site of cell or tissue injury. Continuous inflammatory responses may lead to different types of autoimmune diseases such as RA. The pathological process in RA involves macrophages and lymphocytes migrating to the synovium of joints, causing synovitis. Certain phytochemicals are considered to inhibit the release of inflammatory molecules to suppress inflammatory responses (Shin et al., 2020, p. 5932; Gandhi et al., 2022, pp. 1–15).

***Punicalagin.*** Is the precursor of ellagitannin and has been reported to be the most active polyphenol obtained from different parts of the pomegranate tree (Punica granatum Linn.). Methanolic (and ethanolic) pomegranate peels extract contains a high amount of bioactive compounds, including punicalagin

(10–50 mg⁄g) (Xu et al., 2021, pp. 1–12). Historically, seeds and juices are believed to have been taken as supplements to reduce the clinical symptoms of RA (Singh, Singh, & Mahajan, 2020, pp. 1306–1327). Marques and coauthors (2016) have already revealed that Punicalagin diminished TNF α and interleukin (IL) 6 secretion in macrophages and primary human chondrocytes with lipopolysaccharide (LPS)-induced inflamed RAW264.7. (Marques et al., 2016, pp. 463–1467). Nuclear factor kappa B (NF-κB) is a transcription factor that is activated by inducers such as cytokines in the cytoplasm of various types of immune cells. It migrates to the nucleus where it in turn induces transcription of target genes that mediate inflammatory responses, including those involving cytokines and chemokines. It is worth noting that many findings confirm activated NF-κB can be detected in human and animal arthritis synovium. (Singh, Singh, & Mahajan, 2020, pp. 1306–1327).

Cao et al. (2019, p. 2794) demonstrated that in RAW264.7, in a mouse cultured macrophage cell line that was pre-treated with punicalagin and LPS, punicalagin reduced release of LPS-induced nitric oxide (NO), TNF-α, and IL-6 by suppressing NF-κB and the mitogen-activated protein kinase (MAPK) signaling pathway that is responsible for apoptosis of chondrocytes. These results testify to the anti-inflammatory property of punicalagin via its ability to affect different inflammatory pathways.

***Anthocyanins (ACNs).*** Are a subtype of flavonoids; water-soluble polyphenol compounds and which naturally exist in fruits and vegetables. Pelargonidin, delphinidin, cyanidin, peonidin, petunidin, and malvidin are widespread ACNs, present in many common plants. They have been shown to represent potent anti-inflammatory, anti-oxidant, anti-cancer, anti-obesity and immunomodulatory activity (Salehi et al., 2020, pp. 1–20). The role of oxidative stress as one of the factors in the pathogenesis of RA is well-known. The regulation of oxidative stress by ACNs has been demonstrated in recent studies (Li et al., 2019, pp. 6815–6828; Min et al., 2015, pp. 1–17). The dysregulation of T helper 17 (Th17) cells which secrete proinflammatory IL 17 plays an important role in inflammation of affected joints in RA and may contribute to the destruction of cartilage and bone (Miao, Zhao, & Chen, 2022, pp. 1–9; Min et al., 2015, pp. 1–17). Decreasing the number of Th17 cells and the suppression of Th17 cells differentiation via the effect of oral ACNs has been examined *in vivo* and *in vitro* by Min and coauthors (2015). Furthermore, the authors reported the inhibitory effect of ACNs on osteoclasts via the downregulation of cytokines including IL-1, IL-6, IL-17, and TNF-α *in vitro*. Although these studies suggest ACN therapy could represent a useful, novel approach in moderating inflammatory processes involved in chronic inflammatory disease, the results indicate that the oral bioavailability of ACN is low and its conjugated metabolites are released through bile without systemic distribution. It is worth noting that, not only the chemical structure of ACNs, but factors such as gut microbiota and metabolic process may affect the bioavailability of these natural compounds. Recent data proposes that cyanidin-3-O-glucoside may possess a higher bioavailability than other ACNs (Salehi et al., 2020, pp. 1–20; Kozłowska, & Dzierżanowski, 2021, pp. 1–17).

***Ellagic acid (EA).*** Is a widely-distributed naturally bioactive phenolic agent, found predominantly in berries and nut kernels in different concentrations. The bur of the plant *Castanea sativa Mill* (sweet chestnut), the mesocarp of *Punica granatum L.* (pomegranate) and the fresh weight base of *Rubus idaeus L.* (raspberry) all contain a high EA content. The pronounced biological properties of EA such as anti-inflammatory, anti-oxidant, anti-apoptotic and anti-mutagenic effects have been well-documented. Additionally, the antidiabetic, hepatoprotective, neuroprotective and cardioprotective capacity of EA has been summarized by Sharifi-Rad and coauthors (Sharifi-Rad et al., 2022, pp. 1–24). The effect of EA on various indices and possible mechanisms involved in the pathogenesis of RA has been investigated in Freund's complete adjuvant (FCA)-induced arthritis rats by Fikry and coauthors (2019). Administration of oral EA (50 mg/kg/day) for 20 days in the rats considerably decreased paw edema and levels of chitinase-3-like protein-1 (CHI3L1). CHI3L1 is an inflammatory marker induced via the NF-κB pathway and its over expression by chondrocytes and synovial tissue is associated with the inflammatory process of RA. Moreover, the study showed EA reduced cartilage destruction, synovial hyperplasia and bone erosion generated by Freund's adjuvant. Significant suppression of caspase-3 expression in models treated with EA testifies to the anti-apoptotic property of this biologic compound (Fikry, Gad, & Eid, 2019, pp. 878–886).

A study carried out by Lin and colleagues (2020) assessing the protective effects of EA in osteoarthritis suggests that EA suppresses secretion of iNOs (inducible nitric oxide synthase) and COX-2 (cyclooxygenase) in cultured human articular chondrocytes with IL-1β-induced inflammation. Moreover, they observed that EA could impede the destruction of cartilage surface and decrease Osteoarthritis Research Society International (OARSI) grades in osteoarthritic mice models *in vivo* (Lin et al., 2020, pp. 1–9). The results of the

trial conducted by Ghoochani, Karandish and Mowla (2016, pp. 4377–4381) on 38 patients revealed that the consumption of pomegranate juice, which is rich in EA, markedly diminished the stiffness score and improved cartilage destruction and physical function. Although it has been proposed as a therapy due to its potential benefits and little toxicity to normal cells, poor water-solubility and limited oral bioavailability restrict the efficacy of dietary EA. In this regard, a number of studies are being conducted, specifically focusing on drug delivery systems and formulation strategies to improve the bioavailability of EA. Micronized EA powder particles, amorphous EA dispersion, EA inclusion complexes (in cyclodextrins), EA encapsulated in arene-ruthenium metalla-prism cages, EA-polymers, and chitosan (CS) micro/nanospheres are some examples of such biopharmaceutical technologies aiming to allow for the administration of EA in a more bioavailable form (Zuccari et al., 2020, p. 3353).

***Punicic acid (PA).*** Is known as a conjugated linoleic fatty acid and the main bioactive compound of pomegranate seed oil. Its anti-inflammatory, antioxidant, antidiabetic and anti-cancerogenic properties have been recently reported (Aruna, Venkataramanamma, & Singh, 2016, pp. 16–27). Taherian, Maghsoudi and Vaziri (2018, pp. 31–44) examined *in vitro* the effect of PA on LPS-induced matrix metalloproteinases (matrixins, MMPs) gene expression in synoviocytes. These play a major role in pathogenesis of osteoarthritis by degrading the cartilage's extracellular matrix (ECM). The study revealed that PA reduces MMP9 gene expression, the overexpression of which is associated with activation of nuclear factor-κB (NF-κB) (Li et al., 2012, pp. 2096–2106). This may mediate the anti-inflammatory effect of PA in osteoarthritis.

**Future perspectives.** Research interest in a combination of phytotherapy and conventional, Western medication is rising worldwide. Phytochemicals are being investigated *in vitro*, *in vivo* and to a lesser extent in human trials, for better understanding of their potential benefits as therapy for many diseases. Herbs have demonstrated any ability to influence metabolic and immune system functions. Plant materials have been reported to be useful in the treatment of mental disorders, inflammatory diseases and cancers (Mata, Figueroa, & Navarrete, 2019, pp. 1–142). The established origin of many modern medications in ethnobotanical remedies testifies to the important role of phyto-compounds not only in traditional but conventional medicine. Increasingly, studies are investigating the role of herbal medicine in treating autoimmune disorders (e.g., multiple sclerosis, Crohn's disease, ulcerative colitis, atopic dermatitis, and RA). Preliminary results from many recent studies have shown the effect of immunomodulatory plants on the immune system as immunostimulants and/or immunosuppressors. However, regarding the immunomodulatory power of some bioactive compounds, the result of clinical studies differs from those in experimental models. Thus, the lack of reliable data in clinical studies is the main limitation for supporting experimental evidence. The incompatible anti-inflammatory or proinflammatory properties of these bioactive constituents in different autoimmune disorders further necessitates more supportive clinical trials (Di Sotto, Vitalone & Di Giacomo 2020, p. 468). Assessing the awareness of health care professionals on the safety of herbal medicine has gained growing interest worldwide. Accordingly, due to rising importance of natural products in the medical sphere, health care professionals require training to recognize the pharmacokinetic interactions of concomitant use of herbal medicines with conventional drugs, result of natural remedies overdose, tolerance, hypersensitivity, their impact on different organs, toxicity and teratogenicity (Hasen, & Hashim, 2021, pp. 2001–2008). The importance of health education programs to improve knowledge and awareness of health care providers regarding medicinal plants benefits and safety should be considered as research interest in this area continues to grow.

**Conclusion. In recent years, growing evidence has highlighted the fact that biological agents possess the ability to block inflammatory mediators and modulate the immune system, marking them as candidate drugs for the treatment of chronic inflammatory diseases such as RA. However, planning for more clinical trials to investigate pharmacological potential of herbal medicine is necessary. Although to date natural products are mainly used as nutraceuticals, the treatment of RA by medicinal plants needs more investigation to fully explore their potential as pharmacological agents in the treatment of autoimmune inflammatory diseases.**

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