Impact of Flavonoids in the pathogenesis of Arthritis

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Abstract

Arthritis is an autoimmune disorder that predominantly causes inflammation and impacts peripheral joints. Even though immunosuppressive, NSAIDs are implemented for the management of this disorder but they carry some severe side effects along with them. Therefore, society requires treatment with fewer side effects and powerful anti-arthritic properties, such as flavonoids. These are the most prevalent phenolic compounds found in nature that have potent antioxidant, anti-inflammatory, and immunomodulatory activity and also there is a number of bioactive flavonoids that carry potent anti-inflammatory properties. Nevertheless, only a handful has reached their clinical use but in both clinical and preclinical models of arthritis, flavonoids found in the diet have been shown to reduce swelling in joints and arthritis symptoms. There are only a few scientific studies regarding their mechanisms of action in arthritis. In this chapter, we examine the therapeutic effects of the most prevalent and abundant flavonoid groups on arthritis. The modes of action of the most important flavonoids on the body, which are implicated in the transmission of inflammation markers for arthritis, are addressed.

Keywords: Flavonoids, arthritis**,** antioxidant, anti-inflammatory, immunomodulatory, anti-inflammatory, inflammation.

INTRODUCTION

Arthritis is an autoimmune disorder which involves inflammation in joints. It is a disease that affects the joints and makes them less mobile over time which causes a lot of to the person with the disease. Arthritis is marked by deforming, symmetrical polyarthritis that can be mild or severe [1] along with that pulmonary and serositis inflammation may be observed. Arthritis affected around 0.5-1 percent of persons globally in 2010. It affects women three times more frequently than males, and those of European background are more likely to experience it (1%) than people of Asian and African descent (0.5%)[2]. South Africa, Afghanistan, Pakistan, China, and Argentina have lower disease incidence rates than Western countries. [3].

In accordance with the World Health Organization, 80 percent of arthritis patients are seriously crippled and have a 20-year drop in their life expectancy, which varies depending on therapy, resulting in the reduction of a substantial part of their core life activities[1]. Joint pain and stiffness associated with inflammation around the joint are common early signs of arthritis. The joints that are most frequently affected as arthritis progresses are the wrist, metatarsophalangeal (MTP), proximal interphalangeal (PIP), and metacarpophalangeal (MCP).[4]. Recent investigations on the inflammatory pathways involved in arthritis have led in medicines that target proinflammatory mediators comprising IL-1, IL-6, and IL-17, as well as their receptors. Although they can treat arthritis[5], they can have adverse consequences such as infection, vasculitis, arterial wall inflammation, and cellular inflammation.[6]. Alternative methods of treating arthritis are therefore required. Examples of these methods include the use of natural substances, such as dietary supplements and herbal medicines, which have the ability to reduce the release of inflammatory markers and have anti-inflammatory and immunomodulatory effects. Flavonoids, which are plant secondary metabolites with anti-inflammatory properties, anti-atherogenic, and anti-osteoporotic assets, are one of the natural compounds for the management of arthritis that can be consumed on a regular basis.[7] They are gaining popularity due to their pharmacological action as anti-inflammatory modulators in arthritis. In recent years, a number of plant flavonoid and related polyphenols have been studied using animal arthritis models [8]. This chapter reviews the anti-arthritic effects of quercetins, hesperetins, tea flavonoids, apigenin, kaempferol, nobiletin, myricetin, and luteolin. [8].

Arthritis pathogenesis and treatment

The origin for the development of arthritis is not known clearly, but there has been significant progress in understanding the pathogenesis of the disease due to many recent developments. It is obvious that a weakened immune system contributes significantly to the growth of this disease[9]. It has been proposed that triggering an autoimmune response in synovium, APCs are held responsible [10]. These response is then passed to T-cells, that triggers the release of cytokines and further inflammatory mediators in the joint, which have a significant part in the progress of arthritis. To create mediators of inflammation such as matrix-metalloproteinases (MMP) and improve the function of cell adhesion molecules, macrophages and synoviocytes release IL-1 and tumor necrosis factor.[11]. While CAMs are in charge of drawing inflammatory cells into the synovium, MMPs are known to break down and restructure the extracellular matrix, which causes cartilage, one's own hands, wrists, and feet to degenerate. [13]. Increased cytokine levels in the synovium may trigger the translocation of NF-κB into nuclei, which regulates genes producing pro-inflammatory cytokines and contributes to arthritic inflammation [14]. Nonsteroidal anti-inflammatory drugs, also known as NSAIDs are used to treat arthritis by inhibiting the cyclooxygenase (COX) pathway and lowering prostaglandin (PG) biosynthesis [15]. However, they have been linked to liver, kidney, intestinal, hypersensitive, nervous, hematologic, heart disease., and hepatic adverse events, as well as delayed bone healing.[5]. Glucocorticoids, on the other hand, function by reducing leukocyte counts and inhibiting the generation of immune cells [16].

Last but not least, a range of compounds are included in disease-modifying anti-rheumatic medications, or biological DMARDs, which include hydroxychloroquine, leflunomide, sulfasalazine, cyclosporin A, tofacitinib, chloroquine, and methotrexate [17].These drugs function as immunosuppressants, but because of their immunosuppressive properties, they may also raise the risk of infection. Many medicines, including monoclonal antibodies, direct cytokine inhibitors, and receptor antagonists, are presently being utilized in conjunction with DMARD or biological DMARD therapy to improve the medication response[18]. Anti-TNF and anti-IL-1 medications are examples of further treatments.

Flavonoids in the treatment of arthritis:

Several compounds have been studied for their therapeutic potential in recent years that are been isolated from daily food we intake like vegetables & fruits. Like Flavonoids polyphenols which are isolated from the plants and vegetables are important compounds that should include in our daily diet intake. There are over thousands of flavonoids present in the plants which are a type of plant secondary metabolite and works as a physiological and metabolic regulator [19, 20]. A wide range of foods and drinks, such as coffee or tea, beer, wine, cereals, lentils, berries, herbs, and vegetables and fruits, include flavonoids. Flavonoids can be ingested in high quantities since they are extensively distributed and less harmful when combined with other active plant chemicals. The fundamental structure of flavonoids is determined by their degree of oxidation and central ring saturation. These polyphenolic compounds contain the chemical's heterocyclic aromatic skeleton, known as 2-phenyl benzopyron. The phenylpropanoid pathway converts the amino acid phenylalanine into 4-coumaroyl-CoA, the main component of flavonoids. [19]. Numerous flavonoids with different structural patterns, including as flavones, isoflavones, and anthocyanidins, are produced by the phenylpropanoid metabolic pathway. These structural variations account for the observed variations in bioactivity of these related molecules. Flavonoids have strong anti-inflammatory and antioxidant properties; they also limit the release of pro-inflammatory cytokines, nitric oxide (NO), and eicosanoids, as well as interfering with NF-κ(B) and starting protein-1 (AP-1) signaling [21, 18]. The following is a list of flavonoids that may have anti-arthritic properties.

Quercetin

Quercetin is one type of flavonoid that can be found in broccoli, tea or coffee, green onions, the fruit (such apples), and green leafy vegetables. There is a lot of this antioxidant flavonoid in food.Quercetin is one of the more than 5000 phenolic chemicals that are present in plants naturally. Quercetin and its derivatives have demonstrated potent anti-inflammatory properties across several disease models. This compound has previously been shown to affect many elements of cell activity associated with arthritis.

The effect on the combined state

It has been demonstrated that quercetin therapy inhibits collagenase breakdown in ex-vivo articular cartilage. Furthermore, no clinical parameter of synovial fluid in individuals with arthritis was impacted by the co-administration of quercetin, glucosamine, and chondroitin. It has been shown that treating weight loss caused by arthritis with quercetin and rutin is effective in animal models of the disease, including adjuvant-induced arthritis (AIA) and collagen-induced arthritis (CIA).

[22] [23[24] while out that the application of quercetin or rutin as a treatment improves arthritic scores, decreases paw edema, and improves cartilage regeneration. But only rutin was discovered to be more effective in lowering the clinical scores during the chronic phase of arthritis[25, 26]. In a study conducted in vivo, quercetin administration also decreased the gene expression of MMP-1 and -3 in chondrocytes stimulated by inflammation and inhibited the growth of synoviocytes [27]. In insulin-stimulated RA synovial fibroblasts, quercetin was observed to reduce MMP-1, MMP-3, COX-2, and PGE2 expression and production. Moreover, quercetin prevented IL-1-stimulated RA synovial fibroblasts from expressing NF-κB.[28].

Influence on immune cells

At dosages higher than 25 M and 50 M, respectively, quercetin inhibited B lymphocyte and THP-1 macrophage viability and prevented neutrophil activation [29]. Treatment with quercetin decreased reactive oxygen species formation in neutrophils isolated from individuals with arthritis, but did not alter phagocytic activity or cytotoxicity[30]. Quercetin therapy resulted in a decrease in the articular elastase activity of CIA rats, a marker of polymorphonuclear leukocyte activation and accumulation[25].Research on rutoside therapy in vitro has revealed that NO and TNF-α production is reduced in macrophages isolated from AIA rats given rutoside.

Additionally, rutoside therapy lowered the expression of other proinflammatory genes and the creation of TNF-α, NO, IL-1β, and IL-6. Quercetin decreased TNF-α and nitrites in vitro cultures of isolated AIA rat macrophages. Activated macrophages treated with quercetin produced less nitrite and expressed less inducible NO synthase mRNA [31]. Moreover, the tissues of mice fed a meal containing 5% quercetin had lower levels of TNF-α and IL-1β mRNA than the controls. In vitro infusion of quercetin decreased the amount of NF-κB expression in activated human mast cells. In CIA mice, quercetin dramatically lowered blood levels of NO, PGE2, and monocyte chemoattractant protein-1 (MCP-1).[32] In AIA rats, rutoside decreased the levels of MCP-1, TNF-(, and IL-1(in the serum. Quercetin treatment reduced the generation of TNF-(, IL-1(, and MCP-1 by ex vivo activated macrophages.With an IC50 of 62.4 μM, quercetin inhibited hyaluronidase, COX-1, COX-2, and 15-lipoxygenase (15-LO), among other inflammatory enzymes. It also decreased NO production by macrophages [33, 34]. Peripheral 12- and 15-LO activity as well as NF-κB activation were reduced in AIA rats given quercetin. Treatment with quercetin decreased the amount of NO produced in the joints of CIA rats, as well as the expression of COX-2 and NF-κB. Consequently, a number of recent in vivo and in vitro investigations have demonstrated the strong anti-inflammatory and anti-arthritic properties of the flavonoid quercetin.

It's possible that quercetin primarily lowers inflammation by blocking proinflammatory cytokines like TNF-α and IL-1β. Quercetin also reduced the expression and amount of many MMPs, which demonstrated protective effects for bone and cartilage.

Tea flavonoids

Flavonoids, which include most polyphenols, make up over 35 percent of the dry matter in tea leaves. Both black and green tea include flavonoids that belong to the flavanols class, specifically epicatechin, epigallocatechin, epicatechin gallate, and epigallocatechin gallate.

Effects on joint state

Recent research has shown that the flavonoids in tea, catechin and epigallocatechin gallate, can prevent cartilage explants from being broken down by collagenase. When epigallocatechin gallate was added to enzyme-digested explants and in vitro TNF-induced cartilage proteoglycan degradation, the amount of glycosaminoglycan lost was reduced. The in vitro cartilage degradation activity of IL-1 was reduced by epicatechin and epicatechin gallate. This effect was considerably lessened when TNF-α, IL-1, epicatechin gallate, and epigallocatechin gallate were added to human RA cartilage explants.

It was found that epicatechin gallate, epigallocatechin, and epigallocatechin gallate prevented IL-1 from breaking down type II collagen. However, intraarticular epigallocatechin gallate reduced cartilage degeneration in CIA rats but did not change paw inflammation [35, 36]. The aflavin treatment not only stopped pores from forming, but it also slowed down the rate at which the bone joints of the AIA rodents were degrading.In AIA rats, the combination of epigallocatechin with the strong synthetic steroid dexamethasone reduced paw swelling; the effect of either treatment alone was not as substantial.

While epigallocatechin monotherapy did not diminish serum markers of inflammation, combination therapy did. Additionally, this study discovered that treating AIA rats with either monotherapy or combination therapy with dexamethasone resulted in increased bone mineral density.

Inflammation and bone loss were also significantly reduced by dexamethasone and epigallocatechin treatment. Histopathological indications of AIA, such as reduced joint space, fibrin exudation, pannus development, bone erosion, and synovial proliferation, significantly improved when treated with dexamethasone, epigallocatechin, or both[37, 38]. Epigallocatechin-3-gallate (EGCG) decreased clinical scores and inflammation in obese CIA mice. EGCG reduced ankle circumferences, paw edoema, arthritic severity, and histological changes in CIA and AIA rats [39]. (-)-epigallocatechin-3-galate treatment reduced the higher clinical ratings and foot edema associated with arthritis produced by collagen type II antibody. When animals were given (-)-epigallocatechin-3-gallate, their osteoclast counts and histopathology scores for antibody-induced arthritis decreased. [38].

AIA rats' paw edoema and other haematological abnormalities, such as an elevated white blood cell count, were eradicated with methotrexate/epigallocatechin-3-gallate therapy. Furthermore, radiographic and histological signs of arthritis were reduced in AIA mice undergoing combined therapy with methotrexate and (-)-epigallocatechin3-gallate [40].

The compounds EGCG, theaflavin-3,3'-digallate, and epigallocatechin gallate inhibited osteoclast differentiation in vitro. In osteoclast precursor cells, theaflavin-3, 3'-digallate, and (-)-epigallocatechin gallate all decreased MMP-9 mRNA, MMP-2, and MMP-9 activity in a dose-dependent manner. In the ankles of AIA mice, the tea antioxidant epigallocatechin-3-gallate inhibited osteoclast activity and stopped bone resorption. higher clinical ratings and collagen type II antibody-induced foot edema linked with arthritis. When animals were given (-)-epigallocatechin-3-gallate, their osteoclast counts and histopathology scores for antibody-induced arthritis decreased. [38].

Hesperetins

Citrus fruits contain hesperidin, which is a naturally occurring flavanone glycoside that is generated by the interaction of rutinose and hesperetin (aglycone). Both in vitro and in in vivo studies has demonstrated the potent antioxidant and anti-inflammatory effects of hesperidinmolecules.

Impact of immune cells

In CIA rats, hesperidin decreased cartilage elastase activity, a sign of neutrophil activation and infiltration. AIA rat splenocytes increased their production of IL-2, T cells multiplied, and IL1, IL-6, and TNF-α levels in the peritoneal fluid increased.

Additional flavonoids

effects on the status of the joints

Apigenin (4', 5,7-trihydroxyflavone) treatment decreased the incidence and severity of arthritis in CIA mice. Histopathology showed that hesperidin reduced cartilage macrophage infiltration, inflammation levels, and inflammatory cell infiltration, while apigenin had an anti-arthritic effect in AIA rats.

Conclusions

Flavonoids are a class of chemicals that includes the compounds known as an isoflavones, flavonols, and the flavanones. Because flavonoids can prevent disease, their popularity has grown recently. Hesperetin, also known as ((glucosylhesperidin), and quercetin, also known as quercetin 3-4" (O-(-glucosyl) 1-6-O-(-glucoside, have both been tested on humans. Compared with a limited trial using hesperetin, patients with RA who got quercetin showed some benefit. Because of its positive benefits on RA patients, (-glucosyl hesperidin should be investigated in a larger trial or used as a lead chemical for future development. The investigated flavonoids modulated cytokine and MMP activity and prevented cellular proliferation, cartilage degradation, edoema, inflammatory cell infiltration, pannus development, and bone loss in several animal and cellular models.

The restriction of bone loss may be associated with the suppression of osteoclastic activity and function and the enhancement of osteoblastic function and bone formation. The flavonoids under consideration also had an impact on immunological cells. On the other hand, a decline in cell viability, activity, and maturation was also observed. Among these flavonoids' frequent means of action was decreasing immune cells' cytokine production.

Some of the key mechanisms by which these flavonoids provide anti-arthritic effects in RA include altered pro-inflammatory gene expression, altered recruitment and production of proinflammatory cytokines, modification of proinflammatory enzyme activities, and disruption of macrophage and neutrophil cellular activities.

Numerous in vitro, in vivo, and laboratory animal investigations have shown that flavonoids activate immune modulatory mechanisms against inflammatory mediators and protect against joint injury caused by inflammation. Clinical research on the anti-inflammatory effects of flavonoids in RA is, nevertheless, scarce. Furthermore, not much is known about flavonoids' absorption in people. Moreover, not all of these flavonoids have been evaluated against RA's damaging components. The use of natural product-based therapy for RA may be used either prophylactically or therapeutically. When treating RA, flavonoids might be less harmful and more beneficial. While treating RA, it is inevitable to find new anti-inflammatory drugs.

Future disease-modifying anti-rheumatic treatments for RA might make use of flavonoids. Further investigations to ascertain the possible advantages of these flavonoids in disease mitigation should involve human testing and the examination of their anti-inflammatory mechanisms.

Abbreviations

RA- rheumatoid arthritis
IL- interleukin
AIA- adjuvant arthritis
CIA- collagen induced arthritis

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