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Role of hesperidin, luteolin and coumaric acid in arthritis management: A Review

Trisha Sarkar**Abstract**

Arthritis is one of the most common diseases affecting the elderly population, more than 100 types of arthritis are found with different prevalence and medical symptoms. Out of which osteoarthritis (OA) and rheumatoid arthritis (RA) are the most common ones however no such medical treatment is available to cure the disease. Diet therapy had always played a crucial role in many diseases such as diabetes, cardiovascular diseases and many more. The objective of this review work is to evaluate the therapeutic potential of hesperidin, luteolin and coumaric acid that can be found from our daily diet. These phytochemical has anti-oxidative, anti-inflammatory, immunomodulatory and enzyme inhibitory effects. Scientific evidence revealed that these components exert beneficial effects on RA through several cellular mechanisms including down regulation of pro-inflammatory cytokines such as, IL-6, TNF- α and NF- κ B, inhibition of cartilage degradation with destructive metal proteinases, suppression of oxidative stress and enhancement of antioxidant performance. It can be concluded that hesperidin, luteolin and coumaric acid obtained from our diet can have immense effect to alleviate the effect of rheumatoid arthritis both symptomatically and by stopping RA- induced bone destruction. It can be an effective treatment option however more research is required to understand how these dietary phytochemicals can directly affect rheumatoid arthritis.

Keywords: Phytochemical, luteolin, coumaric acid, hesperidin, arthiritis, rheumatism, arthritis management

Introduction

Arthritis is a disorder of the joints wherein in inflammation of the joints are observed. It can affect one or multiple joints at the same time. It is accompanied by joint pain, stiffness, swelling, and redness of the joints and impairs the ability to perform daily work. More than 100 types of arthritis are present with different medical symptoms and prevalence. Rheumatoid arthritis (RA) and Osteoarthritis (OA) are the most common ones ^[1]. It is becoming a very common disease and is observed in elderly person in most of the cases; however it can also develop in younger population. It is more common among women than men and is also prevalent amongst the overweight and obese population ^[2]. Osteoarthritis occurs when the cartilage that cushions the joints wears away whereas rheumatoid arthritis is a degenerative and autoimmune disease where the body's immune system starts attacking own body tissues. The treatment usually depends in the form of arthritis, its location, severity and persistence. There is no cure for the disease as of now however the pain can be suppressed and further damage can be delayed using a combination of pharmacologic and non-pharmacologic measures. The main aim of the treatment is to reduce the joint inflammation and pain as well as preventing further damage and improve the joint functions.

Extensive researchers are being carried out to find the exact cause of Rheumatoid arthritis; however the exact pathway is yet to be elucidated. Development of RA is caused due to series of complex chain of events. Activated T cells expresses the α 4 β 1-integrin, which binds to vascular cellular adhesion molecule on the surface of venules in tissues which are inflamed, then the activated T cells penetrates into ECF by passing through the endothelial wall ^[3]. Cytokines such as IL-1, IL-6, IL-12, IL-15, IL-23, tumor necrosis factor (TNF), T cell receptor (TCR) and transforming growth factor (TGF) is associated with higher generation of T cells ^[4]. The release of cytokines, especially TNF- α , IL-6 and IL-1, causes inflammation of the synovial.

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Determination of cytokine levels, C reactive protein (CRP), erythrocyte sedimentation rate (ESR), plasma viscosity permits the evaluation of anti-inflammatory effects of drugs. Studies have confirmed that phytochemical reduces the various cytokines level hence reducing the inflammation [5].

Phytochemical are various chemical compounds produced by plants with therapeutic activities such as anti-carcinogenic, anti-inflammatory and anti-oxidant properties. Phytochemical such as phenolic, stilbene and polyphenol compounds, flavonoids, terpenoids, alkaloids, anthraquinones, lignans polysaccharides and peptides is known to have positive effect on managing and treating arthritis. These are dietary phytochemical which are widely available in food from plant origin. In Indian diet, food is rich in both plant and animal origin. From the time immemorial, photochemical have played commendable role in curing and averting different diseases [6]. In this review work, we have reviewed three phytochemical namely Hesperidin, Luteolin and Coumaric acid and attempted to gather all useful information and its relationship with inflammation.

Inflammation and Arthritis

When a part of our body swells up it is considered as inflammation, it can be accompanied by redness of that particular area and surrounding, it is often hot and painful, it is especially a reaction to infection or injury. It can take place in any part of the body. The white blood cells try to fight the foreign particle that has invaded our body which causes inflammation. The white blood cells protect our body from infections by foreign materials such as bacteria and viruses, but in some inflammatory disease, the defense system of our body triggers a response even when no foreign substances are present to fight off, these are known as auto immune disorders. Here, the immune system of the body causes damage to its own tissues, rheumatoid arthritis is one of them in which the immune system attacks the joints of the body causing inflammation in the joints. Rheumatoid arthritis is characterized by hyperplasia and synovial inflammation, auto-antibody production, cartilage and bone destruction [7]. Dietary flavonoids have beneficial effect for preventing inflammation and oxidative stress.

Hesperidin

Hesperidin is a flavanone found in citrus fruits. Chemically it is a flavanone glycoside. Its aglycone form is called hesperetin. The molecular formula is C₂₈H₃₄O₁₅. It is weakly acidic with pure being white needle-like crystals. It is light yellow crystalline powder with melting point being 258-262 °C (soften at 252 °C). It is highly soluble in sodium hydroxide solution, pyridine and dimethyl formamide; slightly soluble in hot glacial acetic acid and methanol; very slightly soluble in acetone, ether, chloroform and benzene. It is odorless and tasteless and barely soluble in water, only 1g can be dissolved in 50L of water [8].

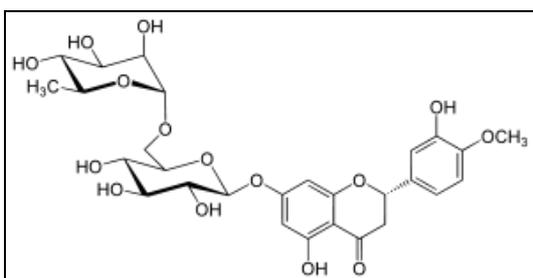


Fig1: Chemical Structure of Hesperidin

Hesperidin is been widely studied as it contains anti-oxidant [9] anti-inflammatory [10, 11], anti-carcinogenic [12] properties, and is also hypolipidaemic [13]. The Anti-Inflammatory property of Hesperidin have been confirmed in animal model of rheumatoid arthritis and also in clinical trials in patients suffering from this disease [14, 15, 16, 17]. All the results of these studies demonstrated a down-regulation of Tumor- necrosis factor (TNF) interleukins (IL) and active macrophages, and up-regulation of the activity of T lymphocytes in the presence of hesperidin. Another study revealed that hesperidin reduces inflammatory pain by targeting transient receptor potential vanilloid (type 1) [TRPV1] receptor activity, oxidative stress, NF-κB activity and cytokine production [18]. Hesperidin has potential anti-oxidant activity and its anti-arthritic effect was evident in a study where the joint inflammation reduced and reduction in articular elastase activity was observed [17]. Reduction in pro-inflammatory cytokines and oxidative stress and augmentation of anti-inflammatory cytokines and antioxidant enzymes has been observed. In conclusion, is suggested that hesperidin may be beneficial in rheumatoid arthritis and can be added to standard anti-rheumatoid therapy since normal intake of this compound along with its derivatives does not show any side effect or any sign of toxicity [19, 20].

Luteolin

Luteolin (3', 4', 5, 7-tetrahydroxyflavone) are naturally occurring flavonoid. They are phenyl substituted chromones (benzopyran derivative) consisting of a 15 carbon basic skeleton chain (C6-C3-C6), with the molecular formula C₁₅H₁₀O₆. It is flavone compound which is found as an integral components of diet. They are quite abundant as constituents of flowering plants, particularly of food plants. It has a potential anti-inflammatory, anti-oxidant, apoptosis inducing and chemopreventive activities [21].

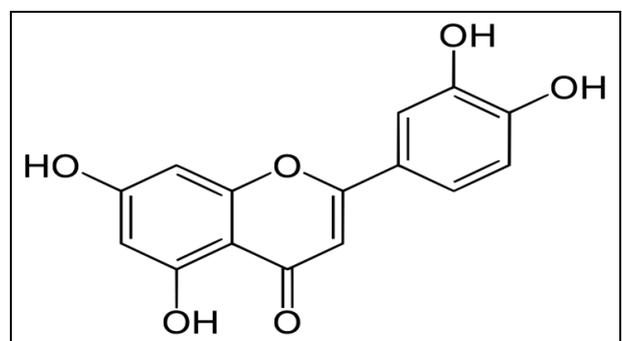


Fig 2: Chemical Structure of luteolin

In a study, it was found that Luteolin significantly inhibited superoxide (SO) anion generation, ROS production. It also inhibited the increase of elastase release, chemotaxis and CD11b expression. It significantly suppressed mitogen-activated protein kinase-1 (MEK-1) and phosphorylation of extracellular signal-regulated kinase (Erk). It reduced the paw edema and paw thickness of the arthritic rats [22]. Another study revealed similar results where Luteolin suppressed TNF-α, IL-1β, IL-6, and IL-17 significantly. All these parameters are potential markers of inflammation and luteolin seemed to significantly suppress these markers. In another study it was found that luteolin reduces synovial hyperplasia and also the infiltration of inflammatory cells as well as protected joint destruction. It also suppressed Caspase-1p10, P2X4, ASC and NLRP1 activity [23, 24]. Number of studies revealed that luteolin reduces oxidative stress and regulate

inflammation [25, 26, 27] so this compound can be used up for the treatment of rheumatic arthritis.

Coumaric acid

Coumaric acid (3-(4-hydroxyphenyl)-2-propenoic acid), a common dietary polyphenol, is also known as 4-Hydroxycinnamic acid, with molecular formula C₉H₈O₃. It is a yellowish green crystalline powder. It is also used for industrial purposes such as producing synthetic indigo, artificial flavours and perfumes. Their biological activities includes antioxidant, anti-cancer, antimicrobial, antiviral, anti-inflammatory, antiplatelet aggregation, anxiolytic, antipyretic, analgesic, and anti-arthritis activities [28] It is a crystalline solid that is slightly soluble in water, but highly soluble in ethanol and diethyl ether [29].

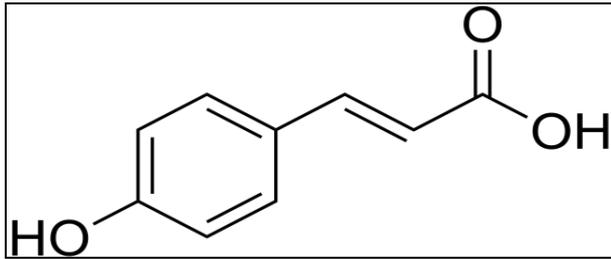


Fig 3: Chemical structure of p-coumaric acid

Coumaric acid has been effective in rat models to treat inflammation. Administration of p-coumaric acid to the arthritic rats brought the altered biochemical and physical parameters to near normal levels, it also reduced the inflammation of the ankle joints by reducing the leukocyte infiltration [30]. Administration of p-coumaric acid reduced the expression of inflammatory mediator TNF- α and circulating immune complexes. The increased cell-mediated immune responses and macrophage phagocytic index was also reduced by administration of this polyphenol [31]. Coumaric acid decreased hypoxia-inducible factor-1 α and NF-kappa B immuno positive neurons significantly (32). It reduced the expression of inflammatory enzymes (iNOS and COX-2), osteoclast genic factors (TRAP and RANKL) and pro-inflammatory cytokines (TNF- α , IL-1 β , IL-6, and IL-17) in arthritic rats [33].

Dietary Sources

Dietary flavonoids shows anti-inflammatory properties in both *in vitro* and on various animal models [34, 35]. Hesperidin, luteolin and coumaric acid are also found from dietary sources, hesperidin can be found in citrus fruits such as orange and lemon. It is also found in grapefruit, apricots, plum, berries etc. It is widely found in the peel of the citrus food, the best source can be 100% orange juice in which the peel, pulp and membranes are pressed and hesperidin is extracted in the juice [36]. Consumption of the orange peel or lemon peel in dried form can be beneficial. It can be added to cakes and pastries which not only enhance the flavor but can increase the nutritive value as well. Luteolin can be found in green leafy vegetables such as garlic stalk, radish leaves, red apple, mustard leaves etc. Garlic stalk and radish leaves are the most abundant source of luteolin [37]. Coumaric acid is found widely in edible plants such as basil, spinach and garlic, it is also found in peanuts, navy beans, tomato, carrot, wine, vinegar and barley grains [38, 39]. Gooseberry, raspberry, strawberry are also good source. It is also found in peer, spinach, chili pepper and onion, it is abundantly found in few mushroom species [40].

Conclusion

Diet therapy is widely used as an effective measure to treat many diseases as it makes the medical treatment more effective. Hesperidin, luteolin and coumaric acid are found in the food components of our daily diet. All the three polyphenols that has been reviewed in this article has shown immense anti-inflammatory properties. All the work cited in this article supports the anti-inflammatory property of these polyphenols. In this review article it is evident that these compounds have several cellular mechanisms including down regulation of pro-inflammatory cytokines such as, IL-6, TNF- α and NF- κ B, inhibition of cartilage degradation with destructive metalloproteinase, suppression of oxidative stress and enhancement of antioxidant performance, through these actions it can exert beneficial effect on arthritis, especially RA. Hence these derivatives can be used effectively for treatment of arthritis as they have promising anti-arthritic effect. Green leafy vegetables and fruits such as apple, pomegranate, orange, grapefruit, cherries, grapes are rich source of polyphenols and can be helpful in this condition. Although the exact mechanisms of this anti-inflammatory activity are not fully elucidated, but several study confirms that there is a correlation between the high intake of food which is rich in these compounds and a down-regulation of the inflammatory response. Further research is required to find the exact correlation. Hence, it can be a safe and effective treatment option in alternate medicine however more research is required to understand how dietary phytochemical can directly affect rheumatoid arthritis.

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