A Review On The Anti-Inflammatory Activity Of Hesperidin, A Bioflavonoid Synthesized By Citrus Fruits

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Abstract
Inflammation is an all-pervasive phenomenon and it is triggered as a countermeasure against pathogenic attack, harmful stimuli and damage to the body tissues. Generally, inflammation peters out once its cause gets terminated. However, persistence of (chronic) inflammation is harbinger of almost all diseases, which that inflammation needs to be tamed to ward off against its harmful effects. The natural products may be good candidates to suppress inflammation. Hesperidin, a bioflavonoid consumed regularly by humans is attributed to possess several medicinal properties including free radical scavenging and anti-inflammatory. This review mainly dwells on its anti-inflammatory property in various study systems. The regular use of hesperidin may be encouraged to stall inflammation related health disorders in humans.

Key words
Inflammation; anti-inflammatory activity; hesperidin; cytokines; free radicals.

Short title
Anti-inflammatory activity of hesperidin

Inflammation

The term ‘inflammation’ is derived from the Latin word “inflammare”, which means to burn. The inflammation is an all-pervasive phenomenon, which is triggered by body tissues against the pathogen attack, harmful stimuli and tissue injury [1]. Inflammation is an innate and adaptive immune response against microbes and parasites that initiate deleterious changes in the tissues [2]. The inflammation is characterized by redness, swelling, heat, pain and loss of function and it was first described by Aulus Cornelius Celsus an encyclopaedist in the First century AD [3]. The inflammation is also a response triggered against the disruption of tissue homeostasis [4].

Inflammation is mainly responsible for the identification and destruction of its source, isolate the source of disturbance, abolish the damaged tissue and restore the homeostasis of the damaged tissue [4,5]. The inflammation is mediated by the concerted action of leukocytes, especially the neutrophils, monocytes and macrophages [5]. These cells secrete a host of factors including serotonin, histamine, eicosanoids, several cytokines, chemokines and plasma derived factors, which dilate the blood vessels and increase their permeability [6]. The inflammatory responses are two types acute and chronic and different mechanisms are involved in their onset [7].

The inflammation is indicted in almost all health disorders. The inflammatory responses are eliminated once the cause of inflammation is terminated. However, sustained inflammation is the major cause of several diseases including diabetes, atherosclerosis, rheumatoid arthritis, hay fever, ischemic heart diseases, leprosy, neurodegenerative disorders, ischemia reperfusion injury, asthma, celiac diseases, tuberculosis, syphilis, inflammatory bowel disease, nephritis, vascularitis, numerous auto-immune diseases and cancer [6,8].

The fact is that any or all health disorders have a direct or indirect link with inflammation. Presently aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) and anticytokine therapy are used to control inflammation [9]. The NSAIDs trigger undesirable adverse side effects on gastric mucosa, liver, heart, kidney, and bronchus [10,11]. This indicates the need of safe and non-toxic alternatives to tame inflammation. The natural products may of great help to reduce the chronic inflammation and inhibit the inflammatory disorder in human beings. Hesperidin, a citrus bioflavonoid which is in regular use as an orange juice may be useful to suppress the inflammation. This review discusses the anti-inflammatory activity of hesperidin a secondary metabolite synthesized mainly by citrus plants.

Hesperidin Actions

The use of dietary ingredients to reduce inflammation or treat inflammation related disorder is an attractive position. The hesperidin (Hesperetin 7-O-rutinoside or Hesperitin-7-rhamnoglucoside) is a bioflavonoid synthesized mainly by many citrus plants as a secondary metabolite, and it is abundantly present in the fruit juices and rinds of these plants [12]. The main function of the hesperidin is to protect citrus plants against fungal and bacterial intrusions [13]. The sweet oranges (Citrus sinensis), tangelos and pulpy orange juice contain the highest amount of hesperidin than the orange juice that has no pulp [14]. Generally, 470-761 mg of hesperidin is present in one litre of orange juice [15]. The hesperidin is converted into its aglycone, hesperitin in the colon by the action of intestinal bacteria, which is subsequently degraded or absorbed [16]. Hesperidin aids in absorption of vitamin C and increases capillary (blood vessels) permeability. It helps to improve hypertension in humans, protects against haemorrhages, infections, heals ruptured capillaries and connective tissues [17].
The analgesic, antiallergenic, antimicrobial, anticancerous, anti-inflammatory, antihypotensive and vasodilating activity of hesperidin have been reported in different study systems [15-21]. The drinking of 500 ml orange juice daily for four weeks consecutively has been reported to trigger the activation of 3422 genes in humans, whereas hesperidin intake in a similar fashion activated only1819 genes in humans [22]. Hesperidin has been reported to be active against atherogenesis, apoptosis, arthritis, infection, *Herpes simplex* virus infection, oxidative stress, neuroinflammatory, bowel disease, platelet and erythrocyte aggregation [23-33]. The hesperidin scavenged free various radicals in vitro and increased the wound healing of irradiated wounds. Oral administration of hesperidin was found to be non-toxic up to a dose of 2g/kg body weight in mice [34,35]. Earlier sub chronic administration of 5% hesperidin for 13 weeks has been reported to be non-toxic in mice [36]. These reports suggest that hesperidin is a multifaceted molecule and possess several activities.

### Free radical scavenging

The free radicals are one of the important mediators of inflammation and the free radical scavenging activity of hesperidin has been studied in vitro. The treatment with different concentrations of hesperidin suppressed the production of *OH and O2*- radicals in a concentration dependent manner and a maximum scavenging of both these radicals was recorded at 500 µg/ml. However, hesperidin did not scavenge DPPH radical up to a concentration of 100 µg/ml, and a further increase in its concentration led to a concentration dependent rise in DPPH scavenging up to 500 µg/ml. The total antioxidant activity using ABTS revealed concentration dependent scavenging of ABTS** radicals up to 200 µg/ml hesperidin, which plateaued thereafter. The nitric oxide (NO) radicals were also suppressed by hesperidin as it showed a dose dependent scavenging of NO** up to 60 µg/ml, which reached an almost steady state thereafter. However, the maximum scavenging of nitric oxide was observed at 400 µg/ml [34].

### Anti-Inflammatory Activity

The anti-inflammatory activity of hesperidin was studied in carrageenan-induced rat paw edema, where treatment of rats with 50 and 100 mg/kg body weight (b. wt.) of hesperidin sub cutaneously (s.c.) reduced the carrageenan-induced paw oedema by 47 and 63%, respectively, within 5 h of its administration. Similarly, treatment of rats with 100 mg/kg hesperidin alleviated the dextran induced rat paw oedema by 33%, without influencing the histamine-induced paw oedema. Hesperidin suppressed the carrageenan-induced pleurisy, where it reduced the volume of exudate and the number of migrating leukocytes by 48 and 34%, respectively of control values. Administration of mice with 100 mg/kg b. wt. hesperidin s. c. reduced acetic acid-induced abdominal constriction by 50%, however, did not affect the tail flick response [37].

Treatment of mice with 100, 200, 300 and 400 mg/kg b. wt. hesperidin suppressed the induction of xylene induced ear edema by 26.03% (10.34±1.05 mg), 34.54 % (9.15±1.09 mg), 47.21 % (7.38±1.2 mg) and 43.63 % (7.88±6.63 mg), respectively in mice. Similarly, administration of mice with 100 mg/kg b. wt. hesperidin significantly reduced the formalin-induced paw edema indicating its anti-inflammatory potential [38].

A study on the of anti-inflammatory activity on the rat air pouch model exhibited that hesperidin treatment of rat pouch injected with carrageenan reduced the carrageenan-induced rise in the lipid peroxidation, glutathione, nitrite and the activities of superoxide dismutase and catalase and TNF-α in the air pouch homogenate. Carrageenan injection into the air pouch induced edema, marked by the enlargement of the pouch wall and the infiltration with neutrophils, macrophages and lymphocytes. Treatment of 50 mg/kg hesperidin S.C. reversed all these changes and the inflammatory cells including neutrophils, macrophages and lymphocytes were conspicuous by their absence indicating that it has blocked the inflammatory response [39].

Treatment of rats with 10 or 25 mg/kg b. wt. hesperidin exerted anti-inflammatory effect in the trinitrobenzenesulfonic acid induced colitis. It reduced the activity of myeloperoxidase and increased the glutathione contents in the colitic rats [40].

Treatment of 100 and 200 mg/kg b. wt. hesperidin to high fat diet fed LDL receptor deficient (LDLr-/-) mice model of atherosclerosis resulted in the inhibition of hepatic steatosis, atherosclerotic plaque area and macrophage foam cell formation. The hesperidin treatment resulted in the down-regulated expressions of acetyl coenzyme A carboxylase alpha (ACCa) and fatty acid synthase (FAS) in the liver. Hesperidin also increased the expression of hepatic ATP-binding cassette transporters G8 (ABCg8), macrophage ATP-binding cassette transporters A1 (ABCA1) and G1 (ABCG1) indicating that hesperidin alleviated the inflammation in LDLr-/- mice and reduced atherosclerosis [41].

The study of anti-inflammatory activity of hesperidin on lipopolysaccharide (LPS)-induced lung inflammation revealed that administration of 200mg/kg b. wt. of hesperidin orally downregulated the LPS-induced expression of various cytokines including TNF-α, IL-1β, IL-6, KC, MIP-2, MCP-1, and IL-12 coupled with the elevated production of IL-4, IL-10. The hesperidin administration reduced the total leukocyte counts; nitric oxide production, iNOS expression in the lungs of LPS treated mice. Hesperidin treatment inhibited the expression of IL-8 in cultured A549 cells and THP-1 cells, whereas the proinflammatory cytokines including TNF-α, IL-1β, and IL-6 were suppressed in THP-1 cells only. The expression of ICAM-1 and VCAM-1 was inhibited in A549 cells treated with hesperidin [42]. Hesperidin also inhibited the LPS induced secretion and gene expression of NO, TNF-α, IL-1β, and IL-6 in BV2 microglial cells [43].

Myocardial infarction is an inflammatory disease and hesperidin administration into the acute myocardial infarction mice markedly depleted the myocardial infarction area, reduced the heart weight/body weight ratio and activity of creatine kinase-MB. Hesperidin treatment also resulted in a decline in the TNF-α, IL-1β, IL-6, MCP-1, ICAM-1, lipid peroxidation and activities of catalase, SOD and caspase-3/99 in mice model of acute myocardial infarction. The expression of p53 and Bax/Bcl-2, was suppressed by hesperidin treatment followed by the induction of peroxisome proliferator-activated receptor-γ (PPAR-γ) in mice with acute myocardial infarction [44].

Bioregulatory molecule nitric oxide plays a crucial role in instigating inflammatory responses and is secreted by neutrophils and macrophages [45,46]. Hesperidin treatment has been reported to reduce the radiation induced secretion of NO estimated as nitrate and nitrite in the regenerating wound of mice at 12 days post-irradiation indicating the anti-inflammatory activity of hesperidin [35].

A study using hesperidin methyl chalcone at 3–100 or 30 mg/kg b. wt. intraperitoneally in male Swiss mice inhibited acetic acid- and phenyl-p-benzoquinone-induced writhing. It also suppressed capsaicin-, complete Freund’s adjuvant- and formalin-induced paw flinching and licking. Hesperidin methyl chalcone did attenuate carrageenan-, capsaicin- and complete Freund’s adjuvant-induced mechanical and thermal hyperalgesia. The exploration of molecular mechanisms revealed that hesperidin methyl chalcone alleviated carrageenan-induced TNF-α, IL-1β, IL-6, and IL-10 production, oxidative stress and NF-κB activation. Hesperidin methyl chalcone did not induce gastric or hepatic injury in a 7 days treatment protocol [47].

### Mechanism of action

The exact mechanism of action to suppress the inflammatory responses by hesperidin is not known. However, the anti-inflammatory action of hesperidin may be mediated by the attenuation of transcriptional activation of NF-κB, and COX-II, which may down regulate the expression of TNF-α, IL-1β, IL-6, ICAM-1, MCP-2, MP-1, iNOS, VCAM-1 and IL-12 (Figure 1). The hesperidin has been reported to subdue the expression of NF-κB, and COX-II and TNF-α, IL-1β, IL-6, ICAM-1, MP-2, MP-1, iNOS, VCAM-1 and IL-12 earlier (Figure 1) [42,44,48,49].

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**Conclusions**

The inflammation is a defense mechanism elicited in response to microbial attack, harmful stimuli and tissue injury. However, prolonged inflammation is the major cause of almost all health disorders including diabetes, cardiovascular, neurological, gastrointestinal, hepatic and kidney disorders and cancer. Therefore, it is necessary to suppress the acute and chronic inflammation to keep the human health in good condition. The hesperidin present in the citrus fruits and their rinds has shown potential as an anti-inflammatory agent as indicated by its ability to inhibit the generation of various free radicals and numerous cytokines including NF-κB, and COX-II, TNF-α, IL-1β, IL-6, ICAM-1, MIP-2, MCP-1, iNOS, ICAM-1, VCAM-1 and IL-12. Since hesperidin is present in various citrus fruits it can be used to inhibit inflammatory disorders as a functional food medicine in humans. Moreover, it is non-toxic, used regularly as orange juice and will be easily acceptable. Therefore, intake of citrus fruit juices/hesperidin may be encouraged to keep humans healthy and protect themselves from inflammatory disorders.

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**Conflict of interest statement**

The author does not have any Conflict of Interest statement to declare.

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