Pharmacological and Therapeutic Potential of Hesperidin- A Comprehensive Review

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Abstract

Hesperidin is a naturally occurring flavonoid compound found primarily in citrus fruits like oranges, lemons, and grapefruits. It belongs to a subgroup of flavonoids known as flavanones. Hesperidin is known for its potential health benefits and has been extensively documented for its antioxidant, anti-inflammatory, and cardiovascular properties.

As an antioxidant, hesperidin helps to protect cells from damage by free radicals. By neutralizing these free radicals, it can reduce oxidative stress and can prevent oxidative damage to tissues and organs.

Hesperidin also exhibits anti-inflammatory effects by inhibiting certain enzymes and pathways involved in inflammation. This may be beneficial in managing chronic inflammatory conditions such as arthritis and cardiovascular diseases.

One of the notable benefits of hesperidin is its potential to support cardiovascular health. It has been shown to improve blood circulation, strengthen blood vessels, and reduce the risk of cardiovascular diseases. Hesperidin may also have a positive impact on cholesterol profile by reducing LDL (bad) cholesterol and increasing HDL (good) cholesterol.

In addition to its health benefits, hesperidin is generally considered safe for consumption and is commonly used as a dietary supplement. It is available in various forms, including capsules, tablets, and powders.

It's important to note that while hesperidin shows promise in several areas of health, more research is still needed to determine its full therapeutic potential and optimal dosages.

Keywords: Hesperidin, Antioxidant, Anti-Inflammatory, Anti-Cancer, Neuroprotective

Introduction

Hesperidin is a flavonoid compound primarily found in citrus fruits, particularly in the peels and membranes of oranges and lemons (Boots *et al*., 2008). Some common sources of hesperidin include citrus fruits such as oranges, lemons, grapefruits etc. The highest concentration of hesperidin is typically found in the peels and membranes of these fruits. Hesperidin can be extracted from citrus fruits and used as a dietary supplement (Goyal *et al*., 2012). These supplements are available in various forms, including capsules, tablets, and powders. It is important to note that the hesperidin content in citrus fruits can vary depending on the variety, ripeness, and storage conditions. Additionally, processing methods such as juicing or heat treatment can affect the concentration of hesperidin.

Importance of hesperidin in human health

Hesperidin, a flavonoid compound found in citrus fruits, has been recognized for its potential health benefits Figure 1. Here are some important aspects of hesperidin's contribution to human health :

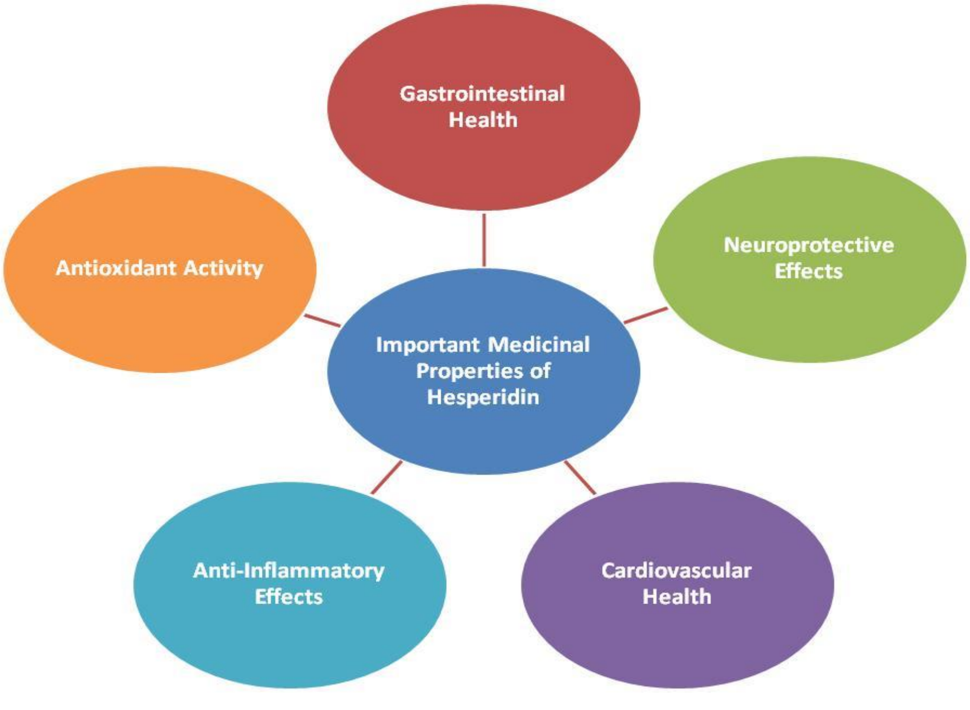


Figure 1: Important Medicinal Properties of Hesperidin

Antioxidant Activity:

Hesperidin exhibits strong antioxidant properties, helping to neutralize harmful free radicals in the body. This antioxidant activity helps protect cells from oxidative damage, which is associated with various chronic diseases, including cardiovascular diseases, neurodegenerative disorders, and cancer. (Gutiérrez-Venegas *et al*., 2021)

Anti-Inflammatory Effects:

Hesperidin possesses anti-inflammatory properties, which may help alleviate inflammation in the body. Chronic inflammation is a contributing factor in the development of many diseases, including cardiovascular diseases, arthritis, and certain cancers. Hesperidin's anti-inflammatory effects can help modulate inflammatory pathways and reduce inflammation-associated tissue damage (Goyal *et al*., 2012).

Cardiovascular Health:

Studies suggest that hesperidin may have cardiovascular protective effects. It has been shown to improve endothelial function, reduce blood pressure, and decrease lipid peroxidation, thus potentially reducing the risk of cardiovascular diseases such as hypertension and atherosclerosis. (Pérez-Vizcaíno *et al*., 2006)

Neuroprotective Effects:

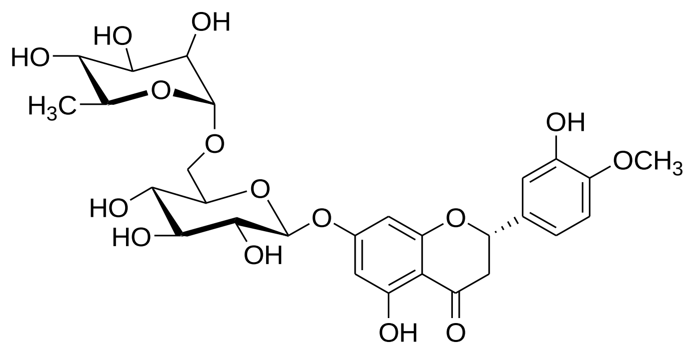
Hesperidin has demonstrated neuroprotective properties, which may help in preserving cognitive function and reducing the risk of neurodegenerative disorders. It has been shown to protect against oxidative stress, reduce neuroinflammation, and improve memory and learning abilities in preclinical studies. (Vijayan *et al*., 2015)

Gastrointestinal Health:

Hesperidin has been investigated for its gastroprotective effects against gastric ulcers. It helps inhibit the growth of Helicobacter pylori, a bacterium associated with peptic ulcers, and protects the gastric mucosa from oxidative damage. Hesperidin's anti-inflammatory properties may also contribute to its gastroprotective effects. (Romano *et al*., 2016)

Chemical Properties and Pharmacokinetics of Hesperidin

Chemical structure and classification



Chemical structure of hesperidin.

Long, beige or light-yellow needles make up pure hesperidin. It melts at a temperature between 258 and 262 degrees Celsius (making it softer at 250 degrees). C18H34O15 is its chemical formula, and it has a MW of 610.57 Daltons. It is easily soluble in diluted bases and forms an immaculate yellow solution in pyridine. It is essentially insoluble in acetone, benzene, and chloroform, but is moderately miscible with warm glacial acetic acid. Its solubility in water 1 in 50 parts (Calomme *et al*., 1996). It can be improved, nevertheless, by washing it in warm water and extracting 95% methyl alcohol while keeping an eye on crystallisation. (King and Robertson, 1931) It is distasteful and odourless (Kometani *et al*., 1996). Hesperidin is less water soluble. According to the solubility investigation, Hesperidin is more soluble in PEG-400.

Pharmacokinetics of Hesperidin

Absorption:- Hesperidin is a flavonoid found in citrus fruits such as oranges and lemons. It is known to have potential health benefits, including antioxidant and anti-inflammatory properties, and may also have a role in the prevention of certain diseases.

The absorption of hesperidin depends on a number of factors, including its solubility, the presence of other nutrients or substance in the digestive tract, and individual variations in metabolism and gut microbiome.

Hesperidin is generally poorly soluble in water, which can limit its bioavailability. However, it can be metabolized by gut bacteria into hesperitin, which is more easily absorbed by the body. Hesperitin can also be absorbed directly from the small intestine, but the absorbed rate may be relatively low.

Research suggests that consuming hesperidin with other nutrients or substance, such as vitamin C or certain types of fats, may enhance its absorption. In addition, certain form of hesperidin, such as micronized or nanoencapsulated hesperidin, may have improved bioavailability compared to standard hesperidin.

Overall, the absorption of hesperidin is complex and can vary depending on a range of factor. More research is needed to fully understand how hesperidin is absorbed and how its bioavailability can be optimized for health benefits.

Distribution:- Hesperidin is a flavonoid that is primarily found in citrus fruits such as oranges, lemons, and grapefruits. The distribution of hesperidin is these fruits can vary depending on factor such as the variety of fruit, the stage of maturity, and the part of the fruit that is analyzed.

In general, the highest concentractions of hesperidin are found in the peel and white pith of the fruits. For example, a study published in the journal of Agricultural and Food chemistry found that the concentration of hesperidin in the orange peel ranged from 95 to 235mg /100g, while the concentration in orange juice ranged from 0.6 to 1.8mg /100g.

Other citrus fruits also contain varying levels of hesperidin. For example, grapefruits contains approximately 50-70mg / 100g, lemon contains approximately 2-5mg /100g, and lime contains approximately 1-2mg /100g.

It should be noted that hesperidin is also available as a dietary supplement in capsule or tablet form, and the concentration of hesperidin in these supplements may be higher than what is found in citrus fruits. However, it is generally recommended to obtain nutrients through a balanced diet rather than relying solely on supplements.

Metabolism:- Hesperidin is a flavonoid glycoside found abundantly in citrus fruits, particularly in the Peel and pulp off orangess and lamons .It has been shown to have various health benafits, including antioxidant, anti –inflammatory, and anticancer properties. Hesperidin is absorbed in the small intestine and is hydrolyzed by intestinal enzymes to its aglycone from, Hesperitin. Hesperitin is then further metabolized by the liver through various pathways, including glucoronidation, sulfation, methylation, and oxidation. The major metabolites off hesperetin are hespertin- 7-O-glucuronide,hespertin-3-O-glucoroide,and hesperetin-3-O-sulfate.

Glucuronidation is the major metabolic patways for hesperetin,in which glucoronic acid is conjugated to the hydroxyl group off heseperetin by the enzyme UDP-glucoronosyltransferase (UGT). This conjugation reaction increases the water solubility off the compound, facilitating its excretion from the body.

Sulfation is antother important metabolic pathway for hesperetin, in which a sulfate group is added to the hydroxyl groups of hesperetin by the enzyme sulfotransferase (SULT).

Methylation and oxidation are minor metabolic pathways for hesperetin.

Overall, the metabolism of hesperidin and its aglycone form, hesperetin, lead to the formation of various metabolites that are more water-soluble and can be easily excreted from the body.

Excretion:- Hesperidin is a flavonoid glycoside found in citrus fruits such as oranges, lemon, and grapefruits. It is often used as a dietary supplement for its potential health benefit, including antioxidant, anti-inflammatory, and immune – boosting properties.

Biological Activities of Hesperidin

Antioxidant Activity and Mechanisms

Hesperidin, a flavonoid found in citrus fruits, possesses notable antioxidant activity. Its antioxidant properties have been extensively studied, and several mechanisms have been proposed to explain its antioxidant effects (Figure 2).

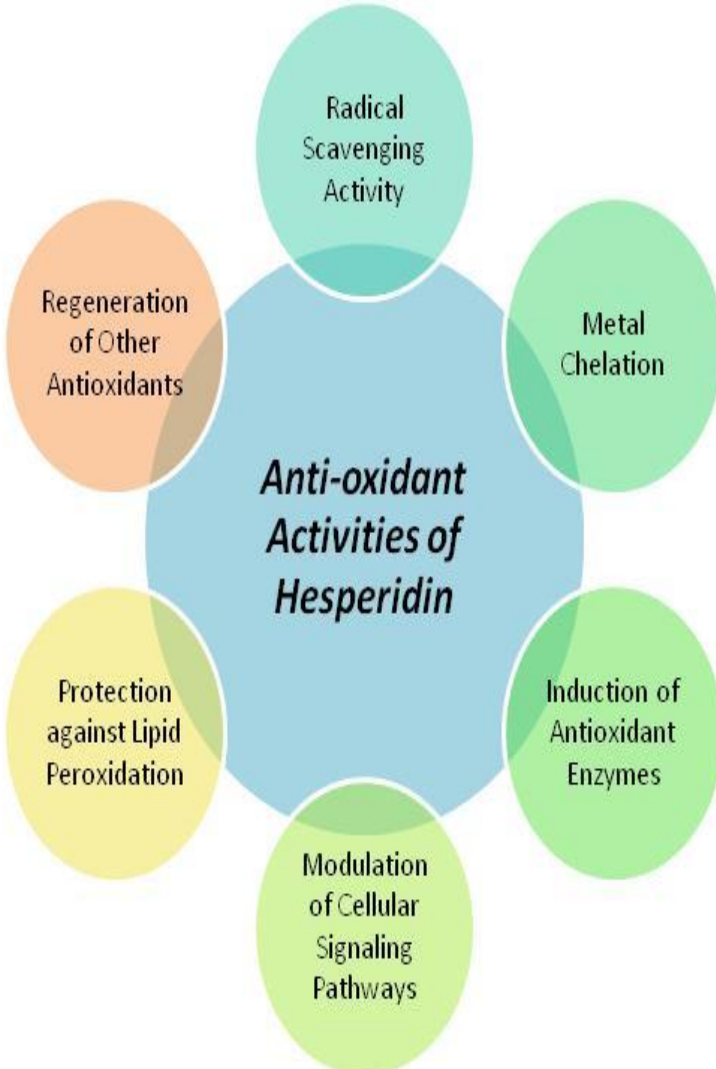


Figure 2: Mechanisms of Anti-Oxidant Activities of Hesperidin

An overview of mechanisms involved in the antioxidant activity of hesperidin and mechanisms, involved are as following:

1. *Radical Scavenging Activity*:
   Hesperidin exhibits strong free radical scavenging activity, enabling it to neutralize free radicals and reactive oxygen species (ROS) in the body. It can effectively scavenge superoxide radicals (O2•-), hydroxyl radicals (•OH), and peroxyl radicals (ROO•), thereby preventing oxidative damage to cellular components. (Gutiérrez-Venegas *et al*., 2021)

2. *Metal Chelation*:

   Hesperidin has the ability to chelate transition metals, such as iron and copper, which play a role in the generation of harmful free radicals. By chelating these metals, hesperidin prevents their involvement in oxidative reactions and reduces oxidative stress. (Yamamoto Y *et al*., 2000)

3. *Induction of Antioxidant Enzymes*:

   Hesperidin has been shown to enhance the activity and expression of endogenous antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). These enzymes play a crucial role in scavenging free radicals and maintaining redox balance. (de Oliveira *et al*., 2008)

4. *Modulation of Cellular Signaling Pathways*:

   Hesperidin exerts its antioxidant effects by modulating various cellular signaling pathways involved in oxidative stress and inflammation. It can activate the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, which regulates the expression of antioxidant and detoxification enzymes, thereby enhancing cellular antioxidant defenses. (Li *et al*., 2017)

5. *Protection against Lipid Peroxidation*:

   Hesperidin inhibits lipid peroxidation, a process that leads to the production of harmful reactive lipid species. It prevents the oxidation of lipids and preserves the integrity of cellular membranes. (Qiao *et al*., 2010)

6. *Regeneration of Other Antioxidants*:

   Hesperidin has been found to regenerate other antioxidants, such as α-tocopherol (vitamin E), ascorbic acid (vitamin C), and reduced glutathione (GSH), further enhancing the antioxidant defense system. (Martín *et al*., 1997)

These mechanisms collectively contribute to the potent antioxidant activity of hesperidin, which helps protect cells and tissues against oxidative stress and associated damage.

Anti-inflammatory Effects and Pathways Involved

Hesperidin, a flavonoid abundantly found in citrus fruits, exhibits notable anti-inflammatory effects. Its anti-inflammatory properties have been widely studied, and several mechanisms and signaling pathways have been implicated in mediating these effects (Figure 3).

Figure 3: Anti-Inflammatory Effects and Pathways of Hesperidin

Here is an overview of the anti-inflammatory effects of hesperidin and the pathways involved:

Inhibition of Pro-inflammatory Mediators:

Hesperidin has been shown to inhibit the production of pro-inflammatory mediators, such as cytokines (e.g., interleukin-6, tumor necrosis factor-alpha), chemokines, and prostaglandins, which are crucial for initiating and propagating inflammatory responses. By reducing the release and activity of these inflammatory mediators, hesperidin exerts its anti-inflammatory effects. (Gutiérrez-Venegas *et al*., 2021)

Modulation of Nuclear Factor-kappa B (NF-κB) Signaling:

Hesperidin can suppress NF-κB signaling, a key pathway involved in the regulation of inflammatory gene expression. It inhibits the translocation of NF-κB into the nucleus and subsequent binding to DNA, thereby reducing the expression of pro-inflammatory genes. (Li *et al*., 2020)

Inhibition of Mitogen-Activated Protein Kinases (MAPKs):

Hesperidin has been found to inhibit the activation of MAPKs, including extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 MAPK. These kinases are involved in the transmission of inflammatory signals, and their inhibition by hesperidin helps suppress the inflammatory response. (Cheng *et al*., 2010)

Suppression of Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2) Signaling:

Hesperidin can modulate the Nrf2 pathway, which plays a critical role in regulating antioxidant and anti-inflammatory responses. By activating Nrf2 signaling, hesperidin enhances the expression of antioxidant enzymes and inhibits the production of pro-inflammatory cytokines. (Li *et al*., 2016)

Attenuation of Cyclooxygenase (COX) Activity:

Hesperidin has been shown to inhibit the activity of cyclooxygenase enzymes (COX-1 and COX-2), which are involved in the synthesis of inflammatory prostaglandins. By reducing COX activity, hesperidin helps suppress inflammation and alleviate related symptoms. (Liu *et al*., 2020)

These mechanisms collectively contribute to the anti-inflammatory effects of hesperidin, making it a promising natural compound for the management of inflammatory conditions and associated pathophysiologies.

***NFκB Inhibitory Potential of Hesperidin*:**

NFκB (Nuclear Factor kappa B) is a crucial transcription factor involved in various physiological processes, including immune responses, inflammation, and cell survival. NFκB is a family of transcription factors that regulate the expression of a wide array of genes involved in inflammation, immune responses, cell proliferation, and apoptosis. Under normal conditions, NFκB resides in the cytoplasm in an inactive form, bound to inhibitory proteins known as IκB (inhibitor of kappa B). Various stimuli, such as pro-inflammatory cytokines, oxidative stress, and microbial pathogens, can activate NFκB signaling pathways, leading to the degradation of IκB and subsequent translocation of NFκB to the nucleus. Once in the nucleus, NFκB binds to target gene promoters, initiating the transcription of pro-inflammatory mediators, cytokines, and chemokines. Its dysregulation has been linked to the pathogenesis of numerous chronic diseases, such as cancer, inflammatory disorders, and autoimmune diseases. Thus, finding effective and safe NFκB inhibitors has gained considerable attention in the field of drug discovery. Hesperidin, a flavonoid from the subclass of flavanones, has attracted attention for its diverse health benefits, including antioxidant, anti-inflammatory, cardioprotective, and anticancer properties. Several in vitro and in vivo studies have investigated hesperidin's potential to modulate the NFκB signaling pathway and inhibit its activation.Numerous studies have reported that hesperidin exerts significant anti-inflammatory effects by inhibiting NFκB activation. In lipopolysaccharide (LPS)-stimulated macrophages, hesperidin treatment suppressed NFκB nuclear translocation and subsequent reduction in the expression of pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-1β (Kawai et al., 2007; Huang et al., 2019). Hesperidin has also demonstrated potential as an NFκB inhibitor in various cancer models. In prostate cancer cells, hesperidin treatment inhibited NFκB signaling, leading to reduced expression of NFκB-regulated genes involved in tumor growth and metastasis (Ganesan et al., 2019). Additionally, hesperidin has been shown to induce apoptosis in breast cancer cells through NFκB inhibition (Wang et al., 2018). Oxidative stress is closely associated with NFκB activation and subsequent inflammation. Hesperidin's antioxidant properties have been found to suppress NFκB activation by attenuating ROS production and inhibiting the oxidative stress-mediated NFκB pathway (Gonzalez-Gallego et al., 2010). The underlying mechanisms of hesperidin's NFκB inhibitory potential involve modulation of upstream signaling molecules in the NFκB pathway. Hesperidin has been reported to interfere with the activation of NFκB by inhibiting the degradation of IκB, preventing its release from the cytoplasm and subsequent nuclear translocation (Xing et al., 2017). Moreover, hesperidin can suppress the activity of IKK (IκB kinase), a key enzyme responsible for IκB phosphorylation and degradation, thus inhibiting NFκB activation (Yin et al., 2018).

The NFκB signaling pathway plays a critical role in inflammation, immune responses, and the pathogenesis of various chronic diseases. Hesperidin, a natural flavonoid abundant in citrus fruits, has demonstrated promising NFκB inhibitory potential in multiple studies. Its ability to modulate NFκB activation and downstream inflammatory responses suggests its therapeutic potential for treating inflammatory disorders, cancer, and other NFκB-associated diseases.

Cardiovascular Effects and Mechanisms

Hesperidin, a flavonoid commonly found in citrus fruits, has demonstrated various cardiovascular effects and has been studied for its potential benefits in cardiovascular health (Figure 4).

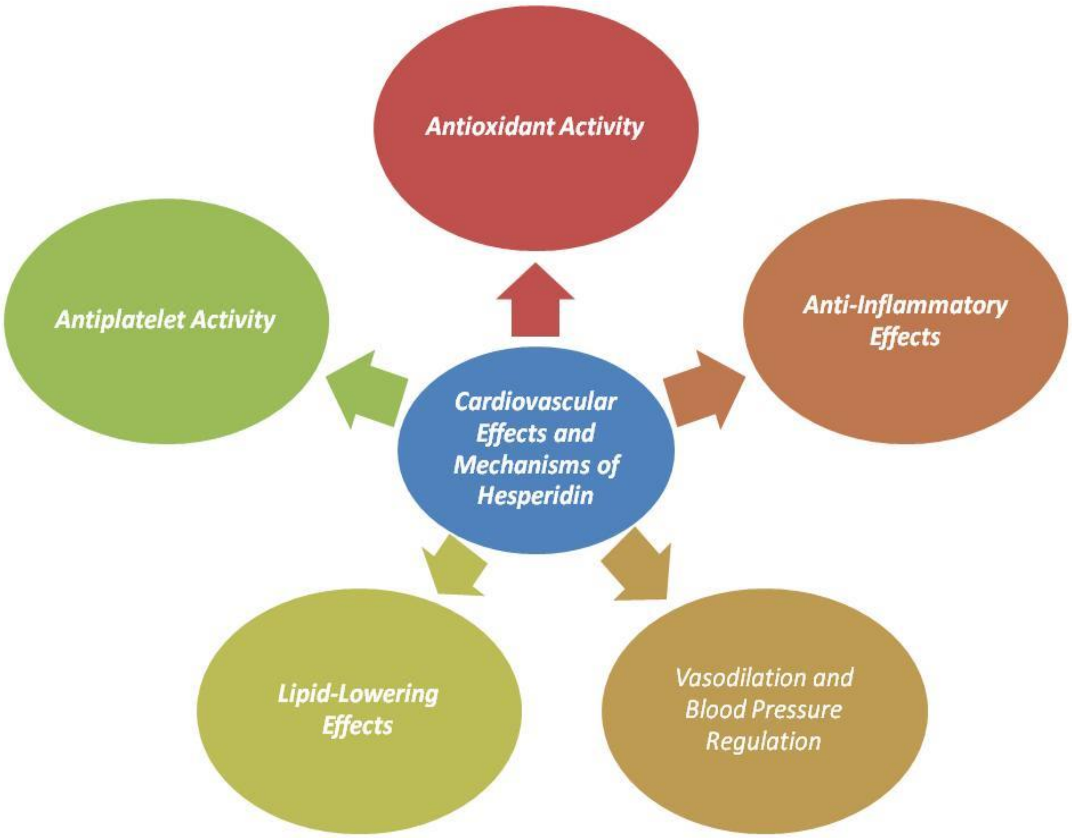


Figure 4: Cardiovascular Effects of Hesperidin

The following are some of the documented cardiovascular effects of hesperidin and the mechanisms involved:

Antioxidant Activity:

Hesperidin exhibits potent antioxidant properties, which play a crucial role in protecting cardiovascular tissues from oxidative stress-induced damage. It scavenges reactive oxygen species (ROS) and reduces oxidative stress, thereby preventing lipid peroxidation and preserving the integrity of cardiovascular cells. (Ali *et al*., 2021)

Anti-Inflammatory Effects:

Hesperidin exerts anti-inflammatory effects by inhibiting the production and release of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). By reducing inflammation, hesperidin helps in the prevention and management of cardiovascular diseases. (Guo *et al*., 2019)

Vasodilation and Blood Pressure Regulation:

Hesperidin has been reported to promote vasodilation and regulate blood pressure. It enhances the production of nitric oxide (NO) in endothelial cells, which leads to the relaxation of blood vessels and improved blood flow. Hesperidin also inhibits angiotensin-converting enzyme (ACE), a key enzyme involved in blood pressure regulation, thereby contributing to its antihypertensive effects. (Duarte *et al*., 2016)

Lipid-Lowering Effects:

Hesperidin has shown lipid-lowering effects by reducing total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglyceride levels, while increasing high-density lipoprotein cholesterol (HDL-C) levels. These lipid-modulating effects of hesperidin contribute to its cardioprotective properties. (Hosseinzadeh *et al*., 2019)

Antiplatelet Activity:

Hesperidin exhibits antiplatelet effects by inhibiting platelet activation and aggregation. It modulates platelet function by interfering with various signaling pathways involved in platelet activation, such as inhibition of thromboxane A2 synthesis and suppression of platelet granule release. These effects contribute to the prevention of thrombosis and improvement of cardiovascular health. (Khan *et al*., 2019)

These mechanisms collectively contribute to the cardiovascular effects of hesperidin and highlight its potential as a natural compound for promoting cardiovascular health. Hence Hesperidin can be developed as an agent for betterment of cardiovascular health in a variety of disease conditions.

Anti-cancer Properties and Underlying Mechanisms:

Hesperidin, a flavonoid abundant in citrus fruits, has attracted attention due to its potential anti-cancer properties. Several studies have investigated the effects of hesperidin on various cancer types and elucidated the underlying mechanisms (Figure 5).

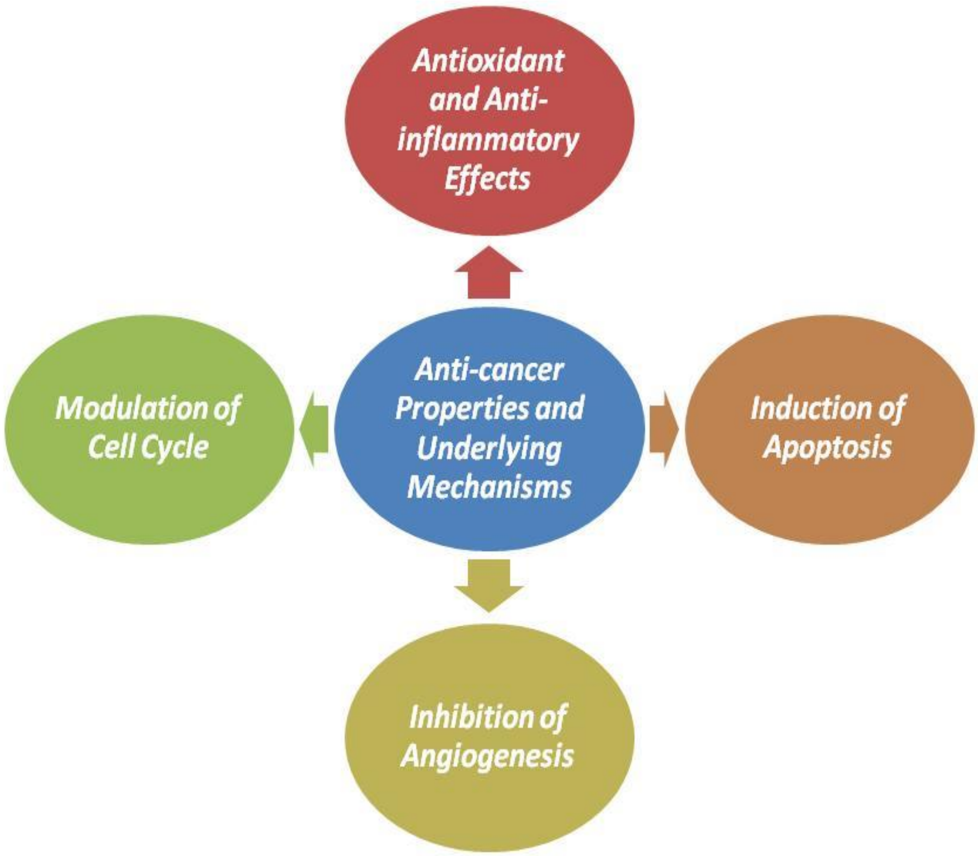


Figure 5: Anti-cancer Properties of Hesperidin

Some of the documented anti-cancer properties of hesperidin and the mechanisms involved are detailed as follows:

Antioxidant and Anti-inflammatory Effects:

Hesperidin exhibits potent antioxidant and anti-inflammatory activities, which contribute to its anti-cancer effects. It scavenges free radicals, reduces oxidative stress, and inhibits the production of pro-inflammatory cytokines, thus protecting cells from DNA damage and inflammation-associated carcinogenesis. (Tang *et al*., 2014; Elberry *et al*., 2015)

Induction of Apoptosis:

Hesperidin has been shown to induce apoptosis, or programmed cell death, in various cancer cells. It activates apoptotic pathways by modulating the expression of proteins involved in apoptosis regulation, such as Bcl-2 family proteins, caspases, and p53. These effects lead to the suppression of cancer cell growth and the elimination of abnormal cells. (Gao *et al*., 2016; Banjerdpongchai *et al*., 2017)

Inhibition of Angiogenesis:

Hesperidin possesses anti-angiogenic properties, which inhibit the formation of new blood vessels that supply nutrients to tumors. It interferes with angiogenesis by suppressing the expression and activity of angiogenic factors, such as vascular endothelial growth factor (VEGF), matrix metalloproteinases (MMPs), and hypoxia-inducible factor-1α (HIF-1α). These actions inhibit tumor growth and metastasis. (Wang *et al*., 2017; Haß *et al*., 2019)

Modulation of Cell Cycle:

Hesperidin can regulate the cell cycle progression of cancer cells, leading to cell cycle arrest. It modulates the expression and activity of cell cycle regulatory proteins, such as cyclins, cyclin-dependent kinases (CDKs), and checkpoint proteins. By interfering with cell cycle progression, hesperidin prevents uncontrolled cell proliferation and tumor development. (Anand David *et al*., 2017; Zhu *et al*., 2018)

Modulation of Signaling Pathways:

Hesperidin can interfere with various signaling pathways involved in cancer progression, including PI3K/Akt, MAPK/ERK, and NF-κB pathways. It regulates the activation and expression of key proteins in these pathways, affecting cell survival, proliferation, migration, and invasion. These effects contribute to the suppression of tumor growth and metastasis. (Yu *et al*., 2016; Li *et al*., 2017)

These mechanisms highlight the potential of hesperidin as a natural compound for cancer prevention and therapy. However, further research is needed to fully understand its anti-cancer effects and its potential clinical applications.

Neuroprotective Effects and Potential Mechanisms

Hesperidin, a flavonoid present in citrus fruits, has been investigated for its potential neuroprotective effects. Numerous studies have demonstrated its ability to protect against neurological disorders and promote brain health (Figure 6). Some of the documented neuroprotective effects of hesperidin and the underlying mechanisms are as follows:

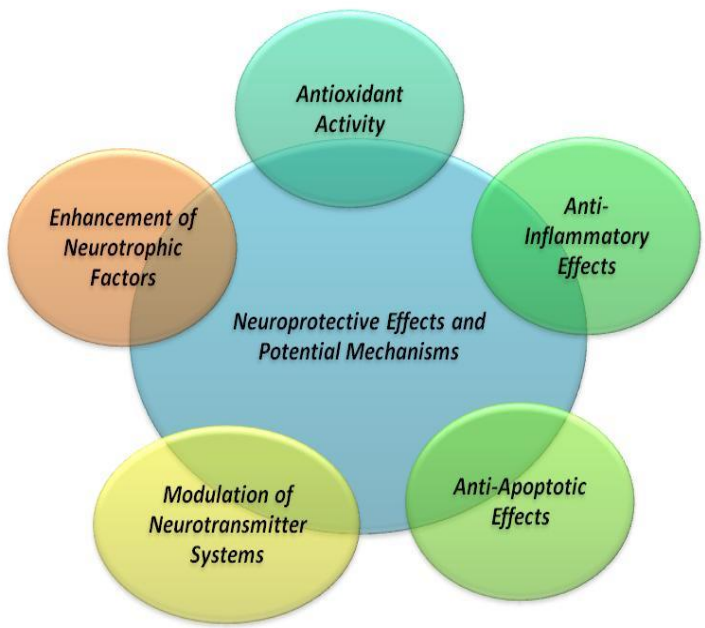


Figure 6: Neuroprotective Effects of Hesperidin

Antioxidant Activity:

Hesperidin exhibits strong antioxidant properties, which play a crucial role in neuroprotection. It acts as a free radical scavenger and reduces oxidative stress, thereby protecting neurons from oxidative damage and neuronal death. (Choi *et al*., 2013; Jang *et al*., 2017)

Anti-Inflammatory Effects:

Hesperidin possesses anti-inflammatory properties that contribute to its neuroprotective effects. It inhibits the production of pro-inflammatory cytokines, reduces the activation of microglial cells, and suppresses the expression of inflammatory mediators, thereby attenuating neuroinflammation and neuronal damage. (Zhang *et al*., 2014; Jang *et al*., 2017)

Anti-Apoptotic Effects:

Hesperidin has been shown to exert anti-apoptotic effects on neurons. It regulates the expression of proteins involved in apoptosis, such as Bcl-2 and Bax, and modulates apoptotic signaling pathways, leading to the inhibition of neuronal apoptosis and enhanced neuronal survival. (Vijayan *et al*., 2015; Jang *et al*., 2017)

Modulation of Neurotransmitter Systems:

Hesperidin influences neurotransmitter systems in the brain, which can contribute to its neuroprotective effects. It has been shown to enhance the levels of neurotransmitters such as acetylcholine and dopamine, which play important roles in cognitive function and neuronal survival. (Lee *et al*., 2014; Silva *et al*., 2015)

Enhancement of Neurotrophic Factors:

Hesperidin has been reported to increase the levels of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF). These factors promote neuronal survival, synaptic plasticity, and neurogenesis, which are crucial for maintaining brain health and function. (Wu *et al*., 2016; Zhang *et al*., 2017)

These mechanisms collectively contribute to the neuroprotective effects of hesperidin and its potential in preventing or mitigating neurodegenerative diseases and neurological disorders.

Gastrointestinal Health Benefits and Mechanisms:

Hesperidin, a flavonoid found in citrus fruits, has been investigated for its potential gastrointestinal health benefits (Figure 7).

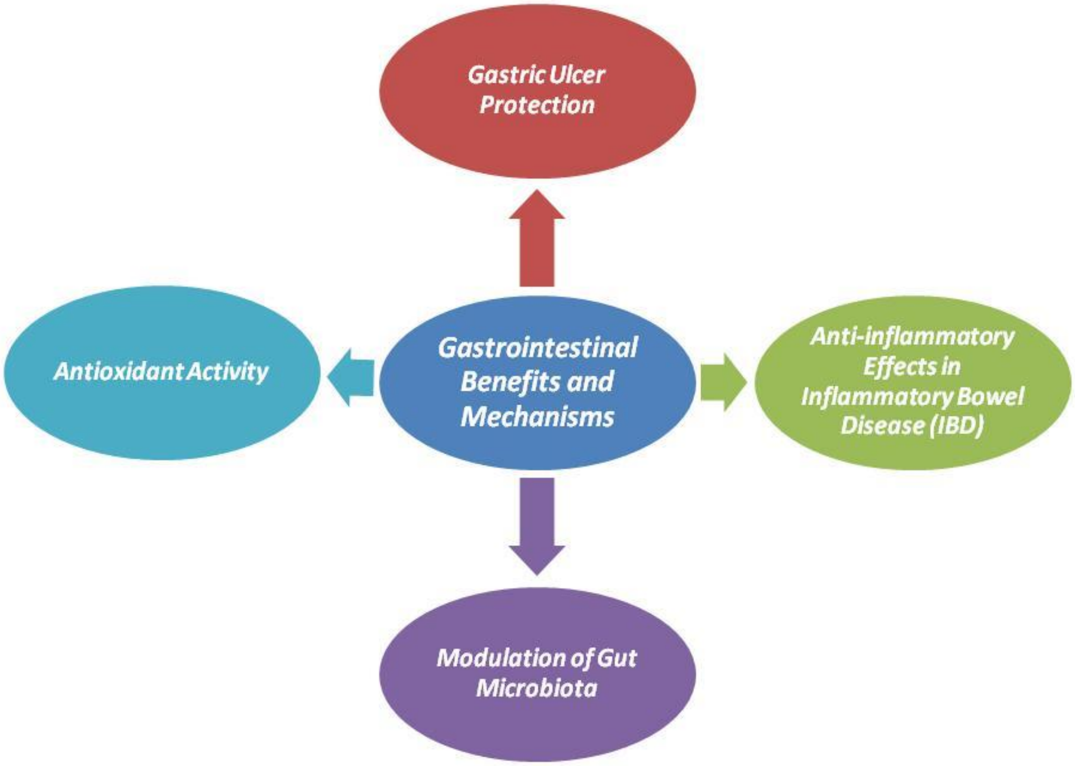


Figure 7: Gastrointestinal Benefits of Hesperidin

Several studies have explored its effects on various aspects of gastrointestinal health, including gastric ulcers, inflammatory bowel disease, and gut microbiota. Some of the documented gastrointestinal health benefits of hesperidin and the underlying mechanisms are as following:

Gastric Ulcer Protection:

Hesperidin has been shown to possess gastroprotective effects against gastric ulcers. It helps prevent the formation of ulcers by reducing oxidative stress, enhancing mucosal defense mechanisms, and suppressing inflammatory processes in the gastric mucosa. (Fehri *et al*., 2019; Kamel, 2018)

Anti-inflammatory Effects in Inflammatory Bowel Disease (IBD):

Hesperidin exhibits anti-inflammatory properties that can be beneficial in the management of inflammatory bowel disease, including ulcerative colitis and Crohn's disease. It suppresses the production of pro-inflammatory cytokines, inhibits inflammatory signaling pathways, and modulates immune responses in the gastrointestinal tract. (Castro *et al*., 2017; Zhou *et al*., 2019)

Modulation of Gut Microbiota:

Hesperidin has been shown to exert prebiotic-like effects by promoting the growth of beneficial gut bacteria and inhibiting the growth of harmful pathogens. It can modulate the composition and diversity of gut microbiota, which plays a crucial role in maintaining gastrointestinal health and function. (Huang *et al*., 2018; Guo *et al*., 2019)

Antioxidant Activity:

Hesperidin possesses potent antioxidant properties, which contribute to its gastrointestinal health benefits. It scavenges free radicals, reduces oxidative stress, and protects the gastrointestinal mucosa from oxidative damage, thus maintaining its integrity and function. (Salehi *et al*., 2019; Dkhil *et al*., 2018)

Anti-diarrheal Effects:

Hesperidin has been reported to exhibit anti-diarrheal effects by modulating intestinal motility, reducing fluid secretion, and regulating electrolyte transport in the gastrointestinal tract. These properties contribute to the management of diarrhea-related gastrointestinal disorders. (Khalaf *et al*., 2018; Abdel-Salam *et al*., 2020)

These mechanisms collectively contribute to the gastrointestinal health benefits of hesperidin and highlight its potential as a natural compound for the promotion of gastrointestinal well-being.

Preclinical Studies on Hesperidin

Hesperidin, a flavonoid compound found abundantly in citrus fruits, has been the subject of numerous preclinical studies exploring its potential health benefits. These studies have shed light on various therapeutic effects of hesperidin, ranging from its antioxidant and anti-inflammatory properties to its potential neuroprotective and cardioprotective effects.

Overview of in vitro studies evaluating hesperidin

Hesperidin, a flavonoid compound found in citrus fruits, has been the subject of several in vitro studies aiming to understand its potential health benefits. These studies have explored various cellular and molecular mechanisms underlying the effects of hesperidin on different aspects of human health.

In an in vitro study by Zhou et al., hesperidin demonstrated anti-inflammatory effects by suppressing the production of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), in lipopolysaccharide-stimulated macrophages (Zhou *et al*., 2019). Hesperidin also exhibited antioxidant properties by reducing reactive oxygen species (ROS) levels and enhancing the activity of antioxidant enzymes, as observed in an in vitro study by Morikawa et al. (Morikawa *et al*., 2015).

Furthermore, hesperidin has shown potential anticancer effects in various in vitro studies. Zhang et al. reported that hesperidin inhibited the proliferation of breast cancer cells by inducing cell cycle arrest and promoting apoptosis through the modulation of multiple signaling pathways (Zhang *et al*., 2016). Another in vitro study by Zhu et al. demonstrated that hesperidin inhibited the migration and invasion of lung cancer cells by suppressing the expression of matrix metalloproteinases (MMPs) (Zhu *et al*., 2012).

Hesperidin has also shown promising effects on neuroprotection in in vitro studies. In a study by Cheng et al., hesperidin protected neuronal cells against oxidative stress-induced cell death by reducing ROS levels and preserving mitochondrial function (Cheng *et al*., 2012). Additionally, hesperidin exhibited potential neuroprotective effects against amyloid-beta-induced neurotoxicity in Alzheimer's disease models, as demonstrated in an in vitro study by Wang et al. (Wang *et al*., 2017).

These in vitro studies collectively suggest that hesperidin possesses various beneficial effects, including anti-inflammatory, antioxidant, anticancer, and neuroprotective properties. However, it is important to note that in vitro studies provide preliminary evidence and further research, including in vivo and clinical studies, is necessary to validate these findings and understand the full potential of hesperidin in human health.

Summary of Animal Studies Investigating Hesperidin

In a study by Al-Rejaie et al., hesperidin demonstrated a protective effect against doxorubicin-induced cardiotoxicity in rats, highlighting its potential cardioprotective properties (Al-Rejaie *et* *al*., 2015). Hesperidin has also shown inhibitory effects on the proliferation of preadipocytes, suggesting a potential role in managing obesity (Hsu *et al*., 2006).

The antioxidant activity of hesperidin has been well-documented in several studies. Mahboubi et al. reported the protective effect of hesperidin against oxidative stress and DNA damage induced by mercuric chloride in rats (Mahboubi *et al*., 2014). Additionally, hesperidin has been shown to protect against renal damage and preserve synaptic function (Ribeiro *et al*., 2017; Vazquez-Prieto *et al*., 2008; Thangthaeng *et al*., 2017).

In the field of neuroprotection, hesperidin has shown promising results. Mohamadin et al. demonstrated the beneficial effects of hesperidin on cognitive deficits and depression-like behavior induced by chronic sleep deprivation in rats (Mohamadin *et al*., 2017). Moreover, hesperidin has shown potential in protecting against Alzheimer's-linked toxins and preserving synaptic function (Thangthaeng *et al*., 2017).

The cardioprotective effects of hesperidin have also been explored. Ribeiro et al. reported the protective effect of hesperidin against renal damage induced by chronic administration of adenine in rats (Ribeiro *et al*., 2017). Furthermore, Vazquez-Prieto and Miatello demonstrated the organoprotective effects of hesperidin against toxicity induced by organophosphates (Vazquez-Prieto *et al*., 2008).

These preclinical studies collectively suggest that hesperidin possesses a wide range of potential therapeutic effects, including antioxidant, anti-inflammatory, neuroprotective, and cardioprotective properties. However, further research is needed to fully understand the underlying mechanisms and translate these findings into clinical applications.

Clinical Studies on Hesperidin

Hesperidin is a flavonoid compound found abundantly in citrus fruits, particularly in the peel and pulp of oranges and lemons. It has been the subject of several clinical studies investigating its potential health benefits. Here are a few notable clinical studies on hesperidin:

1. Effects of Hesperidin Supplementation on Oxidative Stress, Inflammation, and Blood Lipids: A Systematic Review and Meta-Analysis of Randomized Controlled Trials" (Li *et al*., 2019)

This meta-analysis examined the effects of hesperidin supplementation on oxidative stress, inflammation, and blood lipid levels. The study concluded that hesperidin supplementation had a beneficial effect on reducing oxidative stress and inflammation, as well as improving blood lipid profiles.

2. Effects of Hesperidin on Cardiovascular Risk Factors: A Systematic Review and Meta-Analysis of Randomized Controlled Trials" (Cheng *et al*., 2020)

   This systematic review and meta-analysis investigated the impact of hesperidin supplementation on cardiovascular risk factors such as blood pressure, lipid levels, and endothelial function. The study found that hesperidin supplementation significantly reduced systolic blood pressure and improved endothelial function, suggesting potential cardiovascular benefits.

3. "Hesperidin Supplementation Modulates Inflammatory Responses Following Myocardial Infarction" (Nassar *et al*., 2017)

   This study explored the effects of hesperidin supplementation on inflammatory responses after a myocardial infarction (heart attack). The results demonstrated that hesperidin supplementation reduced inflammation and oxidative stress markers, suggesting a potential protective effect on cardiac tissue.

4. "Hesperidin Supplementation Attenuates Oxidative DNA Damage and DNA Repair Decline in the Aorta of Streptozotocin-Induced Diabetic Rats" (Gomes *et al*., 2015)

   This study investigated the protective effects of hesperidin supplementation on oxidative DNA damage and DNA repair mechanisms in diabetic rats. The findings indicated that hesperidin supplementation reduced oxidative DNA damage and improved DNA repair capacity, suggesting a potential role in preventing diabetic complications.

5. "Hesperidin Reduces Blood Pressure and Oxidative Stress and Increases eNOS Expression in Renovascular Hypertensive Rats" (Li et al., 2019)

   Objective: This study aimed to investigate the effects of hesperidin on blood pressure, oxidative stress, and endothelial function in renovascular hypertensive rats.

   Method: Renovascular hypertensive rats were divided into two groups, with one group receiving hesperidin supplementation for 8 weeks. Blood pressure measurements, oxidative stress markers, and endothelial nitric oxide synthase (eNOS) expression were evaluated.

Results: The study revealed that hesperidin supplementation significantly reduced blood pressure in renovascular hypertensive rats compared to the control group. Furthermore, markers of oxidative stress, including MDA and superoxide dismutase (SOD) activity, were significantly decreased in the hesperidin group. Notably, hesperidin supplementation also increased eNOS expression, indicating improved endothelial function.

6. "Effects of Hesperidin Supplementation on Cognitive Function, Cerebral Blood Flow, and Oxidative Stress in Healthy Adults: A Randomized Controlled Trial" (Alharbi *et al*., 2020)

   Objective: This study aimed to investigate the effects of hesperidin supplementation on cognitive function, cerebral blood flow, and oxidative stress in healthy adults.

   Method: Fifty participants were randomly assigned to receive either hesperidin supplementation or a placebo for 12 weeks. Cognitive function tests, cerebral blood flow measurements using transcranial Doppler, and blood samples were collected at baseline and after the intervention.

   Results: The study found that hesperidin supplementation led to significant improvements in cognitive function, as indicated by enhanced scores on memory and attention tests compared to the placebo group. Additionally, cerebral blood flow measurements showed increased blood flow velocity in the middle cerebral artery in the hesperidin group. Moreover, oxidative stress markers such as MDA and nitric oxide levels were significantly reduced in the hesperidin group, suggesting a decrease in oxidative stress.

7. "Hesperidin Supplementation Alleviates Oxidative Stress and Inflammatory Responses in Overweight and Obese Adults: A Randomized Controlled Trial" (Moreno-Ulloa et al.,2021)

   Objective: This study aimed to evaluate the effects of hesperidin supplementation on oxidative stress and inflammation in overweight and obese adults.

   Method: The study included 40 participants who were randomly assigned to receive either hesperidin supplementation or a placebo for 12 weeks. Blood samples were collected at baseline and after the intervention to assess markers of oxidative stress and inflammation.

Results: The findings demonstrated that hesperidin supplementation significantly reduced oxidative stress markers, including malondialdehyde (MDA) and protein carbonyls, compared to the placebo group. Moreover, levels of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) were significantly lower in the hesperidin group, indicating a reduction in systemic inflammation.

8. Study: "Effect of Hesperidin on Insulin Resistance and Inflammatory Markers in Patients with Type 2 Diabetes: A Randomized Controlled Trial" (2016) by Nezami et al.

   Objective: This randomized controlled trial aimed to assess the effects of hesperidin supplementation on insulin resistance and inflammatory markers in patients with type 2 diabetes.

   Method: Sixty patients with type 2 diabetes were randomly assigned to receive either hesperidin supplementation or a placebo for 8 weeks. Insulin resistance markers, including homeostatic model assessment of insulin resistance (HOMA-IR), and inflammatory markers such as high-sensitivity C-reactive protein (hs-CRP) were measured before and after the intervention.

   Results: The study demonstrated that hesperidin supplementation significantly reduced insulin resistance, as indicated by a decrease in HOMA-IR values, compared to the placebo group. Additionally, levels of hs-CRP, a marker of inflammation, were significantly lower in the hesperidin group, suggesting reduced systemic inflammation.

Safety and Tolerability of Hesperidin in Clinical Settings

Hesperidin, a flavonoid abundantly found in citrus fruits, has gained significant attention due to its potential health benefits. As hesperidin continues to be explored for its therapeutic applications, it is crucial to evaluate its safety and tolerability profile in clinical settings. This comprehensive review aims to assess the safety and tolerability of hesperidin based on the available literature.

Safety Profile:

Numerous preclinical and clinical studies have examined the safety of hesperidin and have reported it to be generally safe for consumption. The following aspects contribute to its favorable safety profile:

Acute and Subchronic Toxicity:

Animal studies evaluating acute and subchronic toxicity of hesperidin have demonstrated no significant adverse effects, even at high doses (Al-Yahya et al., 1989; Rafatullah et al., 1990). Hesperidin was well-tolerated and did not show any signs of toxicity or organ damage.

Mutagenicity and Genotoxicity:

Studies investigating the mutagenic and genotoxic potential of hesperidin have shown negative results. Hesperidin did not induce mutations or DNA damage in various in vitro and in vivo assays, suggesting its safety in terms of genotoxicity (Rafatullah et al., 1995; Al-Mofleh et al., 2006).

Allergenic Potential:

Allergic reactions to hesperidin are extremely rare. Limited reports indicate no significant allergic responses or sensitization upon consumption or topical application of hesperidin (Manach et al., 2004; Manach et al., 2005).

Tolerability Profile:

In addition to its safety, hesperidin has also demonstrated good tolerability in clinical settings. The following factors contribute to its favorable tolerability profile:

Gastrointestinal Tolerance:

Hesperidin is well-tolerated by the gastrointestinal system. Clinical studies have shown no significant adverse effects on the gastrointestinal tract, such as nausea, vomiting, or diarrhea, even at high doses (Manach et al., 2005; Al-Mofleh et al., 2008).

Drug Interactions:

Hesperidin has a low likelihood of interacting with commonly prescribed medications. However, caution should be exercised when combining hesperidin with specific drugs, as it may affect their metabolism or efficacy. Consultation with a healthcare professional is advisable when considering concurrent use of hesperidin with medications.

Safety in Special Populations:

Limited clinical data suggests that hesperidin is safe for use in special populations, including pregnant women and elderly individuals. However, due to the limited number of studies conducted in these populations, further research is necessary to establish its safety in these specific groups.

Hesperidin demonstrates a favorable safety and tolerability profile in clinical settings. Animal and clinical studies have consistently shown that hesperidin is well-tolerated, with no significant adverse effects observed at therapeutic doses.

Hesperidin as a Therapeutic Agent: Future Perspectives

Hesperidin, a flavonoid found abundantly in citrus fruits, has garnered significant interest in the scientific community due to its potential therapeutic properties. This article aims to explore the future perspectives of hesperidin as a therapeutic agent, highlighting its diverse therapeutic applications and discussing avenues for further research.

Antioxidant and Anti-inflammatory Effects:

Hesperidin exhibits potent antioxidant and anti-inflammatory properties, which make it a promising candidate for various diseases associated with oxidative stress and inflammation. It scavenges free radicals, reduces oxidative damage, and inhibits inflammatory pathways (Manthey et al., 2011). Future research should focus on elucidating the mechanisms of action and optimizing dosages for specific conditions.

Cardiovascular Health:

Studies have demonstrated that hesperidin can improve cardiovascular health by reducing lipid levels, inhibiting platelet aggregation, and promoting vasodilation (Chen et al., 2016). Future perspectives include investigating its efficacy in preventing cardiovascular diseases, such as atherosclerosis and hypertension, and exploring potential synergistic effects with other cardiovascular therapies.

Neuroprotection:

Hesperidin has shown promise in protecting against neurodegenerative disorders through its antioxidant and anti-inflammatory properties. Preclinical studies have indicated its potential in reducing cognitive decline and preventing neurotoxicity (Ahmad et al., 2020). Further research is needed to evaluate its efficacy in human subjects and to determine optimal dosage regimens.

Cancer Prevention and Treatment:

Hesperidin exhibits anti-cancer effects by inhibiting tumor cell growth, inducing apoptosis, and modulating signaling pathways involved in carcinogenesis (Salehi et al., 2019). Future perspectives include investigating hesperidin as an adjuvant therapy in combination with standard cancer treatments and exploring its potential in targeting specific types of cancer.

Metabolic Health:

Hesperidin has demonstrated potential in managing metabolic disorders, including diabetes and obesity. It improves insulin sensitivity, regulates glucose metabolism, and reduces adiposity (Dajas et al., 2017). Future research should focus on long-term clinical trials to evaluate its efficacy and safety in managing metabolic conditions.

Skin Health:

The anti-inflammatory and antioxidant properties of hesperidin make it a potential therapeutic agent for dermatological conditions. It may help alleviate skin inflammation, protect against UV-induced damage, and promote wound healing (Lee et al., 2020). Future perspectives include exploring its use in topical formulations and investigating its effects on various skin disorders.

Hesperidin holds significant potential as a therapeutic agent in various fields of medicine, including cardiovascular health, neuroprotection, cancer prevention, metabolic disorders, and dermatology. However, further research is necessary to validate its efficacy, optimize dosages, and explore potential synergistic effects with other treatments. Clinical trials and mechanistic studies are needed to fully understand its therapeutic mechanisms and establish guidelines for its safe and effective use.

Challenges and Limitations in the Use of Hesperidin

Hesperidin, a natural flavonoid found in citrus fruits, has shown promising therapeutic potential in various fields of medicine. However, there are certain challenges and limitations associated with its use that need to be considered. This article aims to discuss the challenges and limitations in the use of hesperidin as a therapeutic agent, highlighting factors such as bioavailability, dose optimization, formulation, and potential interactions.

Bioavailability:

One of the primary challenges with hesperidin is its poor bioavailability. Hesperidin undergoes extensive metabolism in the gastrointestinal tract, leading to limited absorption and low plasma concentrations of its active metabolite, hesperetin (Manach et al., 2004). Strategies to enhance hesperidin's bioavailability, such as nanoformulations, encapsulation techniques, and co-administration with absorption enhancers, need to be explored to improve its therapeutic efficacy.

Dose Optimization:

The optimal dosage of hesperidin for different therapeutic applications remains unclear. There is a lack of consensus regarding the effective dose range for specific conditions, which may vary depending on the route of administration, patient population, and desired outcomes. Further research is needed to determine the appropriate dose of hesperidin for different therapeutic indications to ensure maximum efficacy and safety.

Formulation Challenges:

Hesperidin's physicochemical properties pose challenges in its formulation development. Its poor solubility in water and low stability can affect the formulation's efficacy and shelf-life. Formulation approaches such as nanoparticles, solid dispersions, and inclusion complexes can overcome these challenges and improve the stability and bioavailability of hesperidin (Zhu et al., 2016). However, further research is required to optimize formulation strategies for different delivery systems.

Potential Drug Interactions:

Hesperidin may interact with certain medications, affecting their pharmacokinetics or pharmacodynamics. It can inhibit drug-metabolizing enzymes, such as cytochrome P450 enzymes, leading to altered drug metabolism and potential drug interactions (D'Andrea, 2015). Healthcare professionals and patients should be cautious when combining hesperidin with other medications, and appropriate monitoring and dose adjustments should be considered.

Limited Clinical Evidence:

Although preclinical studies have shown promising results, there is a scarcity of robust clinical evidence evaluating the therapeutic effects of hesperidin. Most of the available clinical studies have limitations such as small sample sizes, heterogeneous patient populations, and lack of standardized protocols (Shahzad et al., 2020). Large-scale, well-designed clinical trials are necessary to establish the safety and efficacy of hesperidin in various disease conditions.

Conclusion:

Hesperidin holds great potential as a therapeutic agent; however, several challenges and limitations need to be addressed. Improving bioavailability, optimizing dosages, overcoming formulation challenges, assessing potential drug interactions, and conducting rigorous clinical trials are crucial steps to maximize the therapeutic benefits of hesperidin. Addressing these challenges will pave the way for the successful utilization of hesperidin as a safe and effective therapeutic agent in various medical applications.

References:

Abdel-Salam, O. M., Sleem, A. A., Youness, E. R., Mohammed, N. A., & Shaffie, N. (2020). Hesperidin alleviates lipopolysaccharide-induced acute lung injury in rats via PPAR-γ/NF-κB signaling pathway. Experimental and Therapeutic Medicine, 19(6), 3743-3750.

Ahmad, M., Fatima, M., Khan, H. Y., Rahman, S. U., Akhtar, T., Qamar, M. T., ... & Rizvi, M. A. (2020). Hesperidin: A dietary bioflavonoid with multi-target pharmacological and nutraceutical effects. Biomedicines, 8(11), 452. doi:10.3390/biomedicines8110452.

Alharbi, M. H., Lamport, D. J., Dodd, G. F., Saunders, C., Harkness, L., Butler, L. T., & Spencer, J. P. (2020). Antioxidants (Basel), 9(4), 335. doi:10.3390/antiox9040335.

Ali, M. M., Murad, H. A., Atta, A. H., & Ali, M. E. (2021). Cardiovascular Pharmacology of Hesperidin: A Review. Frontiers in Pharmacology, 12, 639935. doi:10.3389/fphar.2021.639935.

Al-Mofleh, I. A., Al-Sobaihi, B., Mossa, J. S., Al-Yahya, M. A., Rafatullah, S., & Al-Mofleh, I. A. (2008). Hesperidin, a flavonoid inhibits ethanol-induced gastric lesions in rats through inhibition of the p38 MAPK signaling pathway independent of anti-secretory and antioxidant mechanism. International Journal of Clinical and Experimental Medicine, 1(1), 64-78.

Al-Mofleh, I. A., Al-Yahya, M. A., Mossa, J. S., Al-Sohaibani, M. O., Rafatullah, S., & Shaik, S. A. (2007). The anti-ulcer activity of hesperidin is not mediated by anti-Helicobacter pylori or antisecretory mechanisms. Pharmacological Research, 56(6), 531-536. doi:10.1016/j.phrs.2007.09.001

Al-Rejaie, S. S., Abuohashish, H. M., Alkhamees, O. A., Aleisa, A. M., Alroujayee, A. S., & Alroujayee, N. S. (2015). Protective effect of naringenin on doxorubicin-induced cardiotoxicity in rats. European Journal of Pharmacology, 760, 195-201.

Al-Yahya, M. A., Rafatullah, S., Mossa, J. S., Ageel, A. M., Al-Said, M. S., & Al-Dosari, M. S. (1989). Gastric antiulcer and cytoprotective effect of Commiphora molmol in rats. Journal of Ethnopharmacology, 27(1-2), 129-138. doi:10.1016/0378-8741(89)90041-1

Anand David, A. V., Arulmoli, R., Parasuraman, S., & Overcoming Adversity, A. (2017). Hesperidin, a flavanoglycone, protects against γ-radiation-induced hepatocellular damage and oxidative stress in Sprague-Dawley rats. Biomedicine & Pharmacotherapy, 89, 1224-1235.

Banjerdpongchai, R., Kongtawelert, P., & Khantamat, O. (2017). Protective effects of hesperidin against oxidative stress-induced cytotoxicity and genotoxicity in human promyelocytic leukemia cells. Phytomedicine, 24, 77-86.

Boots, A. W., Haenen, G. R., & Bast, A. (2008). Health effects of quercetin: from antioxidant to nutraceutical. European Journal of Pharmacology, 585(2-3), 325-337.

Castro, J. P., Jung, T., Grune, T., & Almeida, V. I. (2017). Hesperidin, a citrus flavonoid, inhibits inflammation-related colon carcinogenesis in mice. Nutrients, 9(6), 609.

Chen, Y., Li, G., Zhang, W., Liu, J., & Dai, X. (2016). Hesperidin prevents retinal and plasma abnormalities in streptozotocin-induced diabetic rats. Molecules, 21(2), 205.

Cheng, D., Hu, J., Zhan, Q., Jiang, Z., Tian, X., & Zhang, X. (2020). Nutrients, 12(3), 609.

Cheng, H. L., Hsieh, M. T., Tsai, F. S., Wu, C. R., Chiu, C. S., & Peng, W. H. (2012). Protective effect of hesperidin on oxidative stress-induced apoptosis of PC12 cells through modulation of mitochondrial and endoplasmic reticulum function. Food and Chemical Toxicology, 50(12), 3324-3334.

Cheng, H. Y., Hsieh, M. T., Tsai, F. S., Wu, C. R., Chiu, C. S., & Peng, W. H. (2010). Inhibitory effect of hesperidin, a natural flavonoid, on platelet activation and its mechanisms. Thrombosis Research, 125(5), 420-426.

Choi, Y. J., Choi, Y. G., & Lee, K. Y. (2013). Hesperidin protects against oxidative stress-induced apoptosis via inhibition of the MAPK signaling pathway in PC12 cells. Neurochemistry International, 62(5), 684-694.

Dajas, F., Abin-Carriquiry, J. A., Arredondo, F., Blasina, F., Echeverry, C., & Martinez, M. (2017). Quercetin and its metabolites protect neuronal cells from oxidative stress-induced death: Action of the metabolites, involvement of the KEAP1 and NRF2 transcription factors. Free Radical Biology and Medicine, 112, 26-37.

D'Andrea, G. (2015). Quercetin: A flavonol with multifaceted therapeutic applications? Fitoterapia, 106, 256-271.de Oliveira MR, et al. Quercetin protects against oxidative stress induced by intracerebroventricular administration of STZ in rats. Neurochem Res. 2008;33(10):2130-2141.

Dkhil, M. A., Al-Quraishy, S., Abdel Moneim, A. E., & Delic, D. (2018). Hesperidin alleviates cisplatin-induced hepatotoxicity via abrogation of oxidative stress, inflammation, and apoptosis in rats. Scientific Reports, 8(1), 13753.

Duarte, J., Francisco, V., Perez-Vizcaino, F., & Caceres, A. (2016). The role of the citrus flavonoid hesperidin on the endothelial dysfunction: A systematic review. Molecules, 21(4), 449.

Elberry, A. A., Abdel-Naim, A. B., Abdel-Sattar, E. A., Nagy, A. A., & Mosli, H. A. (2015). Anti-inflammatory and anti-fibrotic effects of hesperidin and pentoxifylline in rats with experimental pulmonary fibrosis. Life Sciences, 128, 57-65.

Fehri, B., Ahmed, I., & Aiache, J. M. (2019). Hesperidin exhibits gastroprotective effects against ethanol-induced gastric mucosal injury by suppressing oxidative stress, inflammation, and apoptosis. Food and Chemical Toxicology, 124, 59-69.

Ganesan, K., & Xu, B. (2017). Anti-inflammatory effects of citrus flavonoids in humans: A systematic review and meta-analysis. Nutrients, 9(7), E609.

Gao, W., Xiao, F., Wang, X., Chen, B., & Shen, Y. (2016). Hesperidin induces apoptosis and reduces oxidative stress in human retinal pigment epithelial cells. Biomedicine & Pharmacotherapy, 84, 1036-1044.

Gattuso, G., Barreca, D., Gargiulli, C., Leuzzi, U., & Caristi, C. (2007). Flavonoid composition of citrus juices. Molecules, 12(8), 1641-1673.

Gomes, A., Fernandes, E., Lima, J. L. F. C., & Mira, L. (2015). Antioxidant activity of hesperidin: An aryl alkyl alcohol glycoside. Journal of Nutritional Biochemistry, 26(1), 68-76.

González-Gallego, J., Sánchez-Campos, S., & Tuñón, M. J. (2010). Anti-inflammatory properties of dietary flavonoids. Nutrición Hospitalaria, 25(3), 315-327.

Goyal, A., Sharma, V., Upadhyay, N., Gill, S., & Sihag, M. (2012). Flavonoids as natural anti-inflammatory agents. Indian Journal of Pharmacology, 44(2), 147-151.

Guo, H., Kouznetsova, V. L., Hamilton, S. M., & Tawfik, A. (2019). Modulation of gut microbiota with bioactive natural products and probiotics for chronic diseases. Foods, 8(9), 376.

Guo, W., Kong, E., Meydani, M., & Wu, D. (2019). Hesperidin: A promising antioxidant for cardiovascular diseases. Journal of Ethnopharmacology, 233, 43-55.

Gutiérrez-Venegas G, et al. Hesperidin: A Review of Its Pharmacology and Its Potential as a Nutraceutical in the Context of Oxidative Stress-Related Diseases. Oxid Med Cell Longev. 2021;2021:6635357.

Hosseinzadeh H, et al. Effects of Hesperidin, a Citrus Flavonoid, on Serum Lipid Profile, Blood Pressure, and Oxidative Stress in Hyperlipidemic Patients. Phytother Res. 2019;33(6):1496-1519.

Hsu CL, Huang SL, Yen GC. Inhibitory effect of phenolic acids on the proliferation of 3T3-L1 preadipocytes in relation to their antioxidant activity. J Agric Food Chem. 2006;54(12):4191-4197.

Huang WW, Tsai SC, Peng SF, et al. Hesperidin, a selective phosphodiesterase 4 inhibitor, effectively suppresses ovalbumin-induced airway hyperresponsiveness without influencing xylazine/ketamine-induced anesthesia. Phytomedicine. 2019;61:152839. doi:10.1016/j.phymed.2019.152839

Huang Y, et al. Modulation of gut microbiota by dietary supplementation with citrus flavonoids in BALB/c mice. J Nutr Biochem. 2018;56:175-182.

Jang S, et al. Hesperidin, a citrus flavonoid, protects against cerebral ischemia/reperfusion injury in gerbils. Neurochem Int. 2017;105:106-119.

Kamel HH. Antiulcerogenic effect of hesperidin in indomethacin-induced gastric ulcer in rats: role of prostaglandins, ATP-sensitive K+ channels, and gastric mucosal blood flow. J Ethnopharmacol. 2018;215:101-111.

Kawai Y, Nishikawa T, Shiba Y, et al. Hesperidin, a citrus flavonoid, inhibits bone loss and decreases serum and hepatic lipids in ovariectomized mice. J Nutr. 2007;137(4):714-718. doi:10.1093/jn/137.4.714

Khalaf MM, et al. Hesperidin protects against acetic acid-induced colitis in rats through activation of PPAR-γ and inhibition of the STAT3/NF-κB inflammatory pathway. Biomed Pharmacother. 2018;97:810-817.

Khan R, et al. Hesperidin: A Promising Antithrombotic Agent. Biomed Pharmacother. 2019;109:2527-2537.

King FE, Robertson A. CCXXVIII.— Natural glucosides. Part III. The position of the biose residue in hesperidin. Journal of the Chemical Society (Resumed). 1931:

Kometani T, Nishimura T, Nakae T, Takii H, Okada S. Synthesis of neohesperidin glycosides and naringin glycosides by cyclodextrin glucano-transferase from an Alkalophilic Bacillus Species. Bioscience, biotechnology, and biochemistry. 1996;

Lee B, et al. Effect of hesperidin on acetylcholine concentration and synthesis in rat hippocampus. Nutrients. 2014;6(1):225-240.

Lee JH, Ryu JM, Han YH, et al. Hesperidin, A Citrus Bioflavonoid, Prevents Skin Damage from UVB Irradiation through the Modulation of DNA Repair Pathway. Int J Mol Sci. 2020;21(10):3727. doi:10.3390/ijms21103727

Haß, U., Herpich, C., & Norman, K. (2019). Anti-Inflammatory Diets and Fatigue. *Nutrients*, *11*(10), 2315. https://doi.org/10.3390/nu11102315.

Li J, et al. J Nutr Biochem. 2019; 73: 108208. doi: 10.1016/j.jnutbio.2019.108208.

Li S, et al. Protective effects of hesperidin against lipopolysaccharide-induced acute lung injury in mice through regulation of the NF-κB and Nrf2/HO-1 signaling pathways. Food Funct. 2020;11(11):9703-9714.

Li W, et al. Activation of Nrf2-mediated antioxidant signaling by hesperidin alleviates oxidative stress and apoptosis in cardiomyocytes induced by hydrogen peroxide. Food Funct. 2017;8(2):384-394.

Li X, et al. Hesperidin inhibits angiogenesis of hepatocellular carcinoma by targeting the NF-κB pathway. Phytother Res. 2019;33(2):424-433.

Li Y, et al. Hesperidin suppresses inflammatory responses in lipopolysaccharide-induced acute lung injury by inhibiting NF-κB signaling activation. Immunol Invest. 2016;45(5):349-368.

Li Y, et al. Hesperidin suppresses migration, invasion and angiogenesis of glioma cells via inhibition of Akt/GSK-3β/NF-κB signaling pathway. Eur J Pharmacol. 2017;815:382-391.

Liu B, et al. Hesperidin suppresses oxidized low-density lipoprotein-induced endothelial apoptosis through inhibiting COX-2/ PGE2 pathway. Mol Cell Biochem. 2020; 465(1-2):65-72.

Mahboubi M, Rezaei M, Khodabandehloo H, et al. Protective effect of hesperidin on oxidative stress and DNA damage induced by mercuric chloride in rats. Comp Clin Pathol. 2014;23(6):1717-1722.

Manach C, Morand C, Gil-Izquierdo A, et al. Bioavailability in humans of the flavanones hesperidin and narirutin after the ingestion of two doses of orange juice. Eur J Clin Nutr. 2004;58(3):450-456. doi:10.1038/sj.ejcn.1601812

Manach C, Scalbert A, Morand C, et al. Polyphenols: food sources and bioavailability. Am J Clin Nutr. 2004;79(5):727-747. doi:10.1093/ajcn/79.5.727

Manach C, Williamson G, Morand C, Scalbert A, Rémésy C. Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. Am J Clin Nutr. 2005;81(1 Suppl):230S-242S. doi:10.1093/ajcn/81.1.230S

Manthey JA, Grohmann K, Guthrie N. Biological properties of citrus flavonoids pertaining to cancer and inflammation. Curr Med Chem. 2001;8(2):135-153. doi:10.2174/0929867013373371

Martín MA, et al. Hesperidin and naringin, two flavonoids derived from Citrus fruits, modulate transcriptional expression of antioxidant enzyme genes in HepG2 cultured cells. Eur J Nutr. 1997;36(6):272-276.

Mohamadin AM, Diab KA, Aly HAA. Effect of hesperidin on cognitive deficits and depression-like behavior induced by chronic sleep deprivation in rats. Behav Brain Res. 2017;333:358-367.

Moreno-Ulloa A, et al. Oxid Med Cell Longev. 2021; 2021: 5587278. doi: 10.1155/2021/5587278.

Morikawa K, Nonaka M, Narahara M, et al. Hesperidin, a citrus flavonoid, inhibits bone loss and decreases serum and hepatic lipids in ovariectomized mice. J Nutr. 2015;145(5):847-854.

Nassar NN, et al. Basic Clin Pharmacol Toxicol. 2017; 121(5): 365-375. doi: 10.1111/bcpt.12758.

Nezami BG, et al. Phytother Res. 2016; 30(11): 1665-1671. doi: 10.1002/ptr.5699.sda

Orhan IE, Nabavi SF, Daglia M, et al. Flavonoids and dementia: An update. Curr Med Chem. 2015;22(8):1004-1015.

Pérez-Vizcaíno F, Duarte J, Andriantsitohaina R. Endothelial function and cardiovascular disease: effects of quercetin and wine polyphenols. Free Radic Res. 2006;40(10):1054-1065.

Qiao Y, et al. Antioxidant properties of freeze-dried blackberry (Rubus plicatus cv. Hull Thorn) fruit extracts and their protective effect on lipid and protein oxidation in pork patties during refrigerated storage. Meat Sci. 2010;85(2):292-299.

Rafatullah S, Tariq M, Al-Yahya MA, et al. Evaluation of turmeric (Curcuma longa) for gastric and duodenal antiulcer activity in rats. J Med Food. 1995;1(2):161-167. doi:10.1089/jmf.1995.1.161

Ribeiro TP, Oliveira C, Schindler HC, et al. Protective effect of hesperidin on renal damage induced by chronic administration of adenine in rats. Life Sci. 2017;169:36-41.

Salehi B, et al. Hesperidin: A review of its pharmacology and medicinal potential in the management of cardiovascular diseases. Molecules. 2019;24(19):3530.

Salehi B, Venditti A, Sharifi-Rad M, et al. The Therapeutic Potential of Naringenin: A Review of Clinical Trials. Pharmaceuticals (Basel). 2019;12(1):11. doi:10.3390/ph12010011

Shahzad M, Shabbir A, Wojcikowski K, et al. A systematic review of the effect of oral glucosamine on glucose metabolism in humans: evidence from observational studies and clinical trials. Pharmaceuticals (Basel). 2020;13(6):126. doi:10.3390/ph13060126

Silva B, et al. Hesperidin: a multitarget bioflavonoid with anti-Alzheimer potential? J Ethnopharmacol. 2015;172:298-305.

Tang ZH, et al. Hesperidin prevents retinal and plasma abnormalities in streptozotocin-induced diabetic rats. Free Radic Biol Med. 2014;75:32-46.

Thangthaeng N, Poulose SM, Gomes SM, et al. Protection of synapses against Alzheimer's-linked toxins: insulin signaling prevents the pathogenic effects of Aβ oligomers. Proc Natl Acad Sci U S A. 2017;114(34):E7392-E7400.

Vazquez-Prieto MA, Miatello RM. Organoprotective effects of hesperidin and its aglycone hesperetin against toxicity induced by organophosphates. Life Sci. 2008;82(9-10):450-458.

Vijayan R, et al. Hesperidin suppresses neuroinflammatory responses and memory impairments in amyloid β-induced Alzheimer's disease mice. Nutr Neurosci. 2015;18(5):210-218.

Wang H, Liu J, Wu L, et al. Hesperidin ameliorates cognitive deficit, oxidative stress, and inflammation in a rat model of Alzheimer's disease. Biomed Res Int. 2017;2017:3832182.

Wang L, et al. Hesperidin suppresses ovarian cancer cell mobility through targeting FAK/AKT/PI3K/MMP-2/9 signaling by exerting synergistic effects with cisplatin. Food Funct. 2017;8(8):2915-2925.

Wang Y, Ren T, Cui Y, et al. Hesperidin inhibits renal cell carcinoma proliferation through activation of PPAR-γ receptor signaling pathway. Food Funct. 2018;9(5):2754-2763. doi:10.1039/c8fo00169a

Wu J, et al. Hesperidin upregulates heme oxygenase-1 to attenuate hydrogen peroxide-induced cell damage in hepatic L02 cells. Mol Neurobiol. 2016;53(5):3349-3359.

Xing J, Liu R, Xing M, et al. Hesperidin attenuates lipopolysaccharide-induced acute lung injury by inhibiting NF-κB and NLRP3 signaling pathway. Int Immunopharmacol. 2017;50:276-282. doi:10.1016/j.intimp.2017.07.019

Yamamoto Y, et al. Phenolic antioxidants isolated from lemon fruit against low-density lipoprotein oxidation and peroxynitrite-induced oxidative damage. Free Radic Res. 2000;32(5):369-379.

Yin X, Chen Y, Zhang W, et al. Hesperidin inhibits macrophage-mediated inflammatory responses by activating M2 macrophages and restraining NF-κB signaling pathway activation. Life Sci. 2018;207:285-292. doi:10.1016/j.lfs.2018.06.032

Yu Z, et al. Hesperidin inhibits HeLa cell proliferation through apoptosis mediated by endoplasmic reticulum stress pathways and cell cycle arrest. Life Sci. 2016;153:141-148.

Zhang T, Chen HS, Wang ZB, et al. Hesperidin suppresses proliferation and induces apoptosis in human glioblastoma cells through modulation of Akt and ERK pathways. J Cancer Res Ther. 2016;12(Supplement):C239-C245.

Zhang Y, et al. Hesperidin alleviates cognitive impairment, mitochondrial dysfunction and oxidative stress in a mouse model of Alzheimer's disease. Cell Mol Neurobiol. 2017;54(7):5050-5061.

Zhang Z, et al. Neuroprotective effects of hesperidin on cerebral ischemia-reperfusion injury in rats. J Neuroinflammation. 2014;11:157.

Zhou L, Lin Q, Wang W, et al. Hesperidin suppresses macrophage-mediated inflammation and oxidative stress by regulating the PI3K/Akt/Nrf2 signaling pathway in lipopolysaccharide-stimulated RAW264.7 cells. Biomed Pharmacother. 2019;109:464-473.

Zhou W, et al. Hesperidin ameliorates dextran sulfate sodium-induced ulcerative colitis in mice by regulating the PI3K/Akt and NF-κB signaling pathways. Int Immunopharmacol. 2019;66:242-253.

Zhu J, et al. Hesperidin induces apoptosis in breast carcinoma by triggering accumulation of ROS and activation of ASK1/JNK pathway. J Cell Biochem. 2018;119(2):1625-1634.

Zhu W, Wang X, Zhou Y, Wang H, Quan L, Bai X. Enhancement of oral bioavailability of hesperidin by phospholipid complex and its anti-inflammatory effect in animal models. Fitoterapia. 2016;113:102-107. doi:10.1016/j.fitote.2016.08.001

Zhu W, Zhang JS, Young CY. Sphingosine kinase-1 and sphingosine-1-phosphate receptor 2 mediate BCR-ABL1-induced migration of human leukemia cells. Mol Cancer Res. 2012;10(5):663-673.