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# Flavonoids: An Answer to Chronic Diseases

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***Abstract***

*It has been shown that inflammation is closely associated with the onset or exacerbation of quite a few non-communicable human diseases. Several chronic diseases, such as cancer, diabetes, cardiovascular dysfunction and central nervous system damage are also developed following tissue injury produced by the high fragments of low-grade inflammation surrounding a compromised tissue or organ due to its acquired genomic changes. Current therapies for many of these diseases are associated with undesirable, and at times more severe side effects than the actual condition leaving little choice but to seek cheaper options that would be less toxic; this has thus prompted a need for safe treatments. Flavonoids and their compounds have been used in traditional medicine wrongly before ethnomedicines, also for a wide variety of human diseases with use continuing to this day. The aim of this review is to showcase the role of flavonoids which help in reducing inflammation in several chronic illnesses, including diabetes, cancer, heart disease, and neuroinflammation.*

**Keywords**: Cancer, chronic disease, diabetes, flavonoids, inflammation

## INTRODUCTION

Numerous disorders can be caused by cellular inflammation, which can either stimulate cells to develop different types of tumors or cause premature cell death that damages certain organs [1]. Chronic inflammation has been linked to several diseases, including diabetes, heart disease, cancer, digestive disorders, autoimmune diseases, and neurological disorders. Since inflammation is the immune system's protective response to invasive pathogens or endogenous signals like damaged cells, it has long been associated with the symptomatology of infectious conditions [2].

Polyphenols are often categorized as flavonoids (pigments) and phenolic acids. They are primarily present in plant-based foods and beverages including fruit juices, tea, coffee, cocoa, and red wine, although they can also be found in vegetables, cereals, and chocolate. Studying polyphenols is difficult since they are abundant in various foods and have a variety of biological functions. Current research suggests that polyphenols may help avoid chronic illnesses [3]. With their wide range of biological activity and desirable characteristics like antioxidant, anti-mutagenic, anti-inflammatory, and antiviral activities, these substances offer an invaluable collection of substances that can be utilized in the development of therapeutic entities. The possible anti-inflammatory properties of flavonoids in relation to several chronic illnesses. After that, we'll quickly review apigenin's established anti-inflammatory qualities to evaluate its potential as a treatment candidate for long-term neuroinflammatory disorders. Apigenin is a relatively less toxic flavonoid [4].

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## PREVENTIVE ACTIONS OF FLAVONOIDS AGAINST DISEASES

Flavonoids have proved to be a good dietary supplement that fosters health and inhibits disease. Flavonoids have been shown to have preventive

effects against a variety of disease conditions, including cancer and cardiovascular disease, in epidemiological, clinical, and animal research. Additionally, flavonoids demonstrate various biological activities like antibacterial, antiviral and anti-inflammatory properties. Blood platelet aggregation, vascular reactivity, and lipoprotein oxidation have all been linked to atherosclerosis by flavonoids. It is demonstrated that flavonoids' antioxidant, antithrombotic, anti-inflammatory, and hypolipidemic qualities significantly contribute to the decreased cardiovascular death linked to increased flavonoid consumption. Because of this, flavonoids are currently the subject of a lot of interest in both nutrition and medicine [5].

## CLASSIFICATIONS OF FLAVONOIDS

The detailed classification of flavonoids, their dietary sources, chemical compounds and biological functions are summarized in Table 1.

**Table 1**. Classification of Flavonoids

| Class of flavonoids | Dietary Sources | Compound | Biological Function |
|---|---|---|---|
| Flavanol | Tea, red grapes | Catechin, Epigallocatechin | Anti-carcinogenic |
| Flavone | Fruit skins, red pepper, and tomato skin | Apigenin, Chrysin, and Luteolin | Anti-inflammatory, anti-carcinogenic, neuroprotective |
| Flavonol | Onion, red wine, olive oil, berries, and grapefrui | Quercetin, Kaempferol, Myricetin, and Fisetin | Antioxidant, anti-inflammatory, neuroprotective reduce risk of vascular disease |
| Flavanone | Citrus fruits, grapefruits, lemons, and oranges | Hesperetin, Naringenin | Blood lipid-lowering and cholesterol-lowering agents, antiviral, antioxidant |
| Isoflavone | Soyabean | Genistin, Daidzin | Anti-inflammatory, anti-cancer |
| Anthocyanidin | Cherry, Elsberry, and strawberry | Apigenidin, Cyanidin | Anti-inflammatory, antioxidant, anticancer, cardioprotective |
| Flavanonol | Limon, aurantium, Milk thistle | Taxifolin, Silibinin | antioxidant, anti-inflammatory, neuroprotective, antiallergic, antitumor |

## HEALTH BENEFITS OF FLAVONOIDS

The phytochemicals extracted consists of many flavonoids which are natural compounds and possesses many inhibitory activities against diseases. Antioxidant, anti-inflammatory, antiviral, anti-mutagenic, and anti-allergic qualities are a few of these. The hydroxyl groups in flavonoids enable these chemicals to scavenge and stabilize free radicals by complexation with oxidizing species, therefore mitigating oxidative damage, a characteristic of numerous chronic illnesses. In this review, we examine how flavonoids affect different inflammatory processes that either initiate or worsen chronic illnesses.

### Flavonoids in Disease of Chronic Inflammation

A vast range of physiologically active substances, known as flavonoids, have been utilized for thousands of years as constituents of different pharmaceutical formulations to treat a variety of human ailments. Chronic persistent inflammation is the cause of the development of most non-infectious disorders or a major contributing factor in their worsening. We will now examine the unique roles that flavonoids play in preventing numerous inflammatory processes that underlie a number of chronic illnesses, including obesity, cancer, and neuroinflammation. Antioxidant resveratrol appears to influence inflammatory processes. It may have the ability to prolong life by increasing the production of an enzyme called sirtuin 1, which can stop the start of programmed cell death, or apoptosis. The anthocyanins and catechins, including epigallocate-chin-3-gallate (EGCG), are two types of flavonoids [6].

 

**Uses of Flavonoids in Cancer**

Uncontrolled inflammation that lasts for a long time produces toxic reactive oxygen species (ROS) that can damage DNA and alter the genome, which can trigger the development of tumors. Alongside proangiogenic growth factors like VEGF and cytokines, there is also a constant production of inflammatory mediators like TNF, IL-1α/β, IL-6, and IFN-γ that encourage tumor neovascularization, which provides the much-needed blood supply to nourish the expanding tumor. Lastly, the creation of matrix metalloproteinases (MMPs), which are enzymes that degrade extracellular matrix, is one way that inflammation encourages the spread of tumors. Numerous studies have shown that flavonoids can scavenge free radicals, regulate cellular metabolism, and prevent illnesses associated with oxidative stress. A growing body of research indicates that many flavonoids have anticancer properties, but the exact chemical pathways behind these effects are yet unknown. Cancer is a diverse disease that grows aberrant cells that infiltrate and spread to other parts of the body due to unchecked proliferation and a disrupted cell cycle. The primary internal causes of cancer are oxidative stress, hypoxia, genetic mutations, and loss of apoptotic function; the external causes are linked to increasing stress, pollution, smoking, radiation, and UV radiation exposure. The primary features of cancer cells include altered metabolism, disrupted cell cycles, frequent mutations, immune response resistance, persistent inflammation, metastasis formation, and angiogenesis stimulation [7].

There is growing evidence that suggests different degrees of mitochondrial malfunction and metabolic changes are what cause cancer, making it a metabolic disease. Reactive oxygen species (ROS) production, metabolic control, cell death signaling, and the production of cellular energy are all crucial functions of mitochondria. The primary metabolic changes in tumor cells include elevated ROS production, altered lipid metabolism, enhanced aerobic glycolysis, and disrupted enzyme activity. As a direct result, the extracellular environment becomes more acidic and conducive to inflammation, mitochondria are hyperpolarized, glutamine-driven lipid biosynthesis increases and upregulates the pathways involved in the initiation and metastasis of tumors, cardiolipin levels in membranes decrease, impairing enzyme activities, and these effects are correlated with the invasiveness and malignancy of cancer cells.

**Applications of Flavonoids in Diabetes**

Long linked to the development of type 1 diabetes, chronic low-grade inflammation has more recently been linked to the formation and/or aggravation of type 2 diabetes, or diabetes mellitus. Insulin resistance and decreased insulin production are linked to type 2 diabetes. Type 2 diabetes is characterized by nutrient excesses that lead to oxidative stress, endoplasmic reticulum stress, lipid and amyloid deposition, lipotoxicity, and glucotoxicity brought on by inflammatory processes. Hyperglycemia and increased free fatty acids are examples of these nutritional excesses. It is believed that metabolic dysregulation linked to diabetes causes proinflammatory responses in macrophages found in the vasculature, islets, and adipose tissue; the degree of these macrophages' infiltration into adipocytes is directly correlated with the size of the cells. The activation of NLRP3 inflammasome and thioredoxin-interacting protein induces cellular stressors by releasing elevated levels of IL-1β, which in turn contributes to insulin resistance and β-cell malfunction. Acute-phase proteins such serum amyloid A (SAA) and C-reactive protein (CRP) are also produced by adipocytes, endothelial cells, and macrophages in response to increased IL-6 levels. Furthermore, the adipose tissue releases proinflammatory cytokine TNF-α, which raises free fatty acids and promotes lipolysis. characteristics of flavonoids that support its application as an adjunctive therapy for diabetic mellitus. Flavonoids have been shown to reduce insulin resistance, hyperglycemia, oxidative stress, stress-sensitive signaling pathways, and inflammatory processes as depicted in Figure 1. They can also alter the metabolism of fats and carbohydrates. Experiments in diabetic rodents have revealed that flavonoids like hesperidin, chrysin and rutin can improve glucose intolerance, insulin resistance and hyperglycemia by reducing concentrations of inflammatory cytokines. Diabetes mellitus can eventually result in secondary damage to the patient's heart, kidneys, eyes, and nerves, among other organs. In addition to mitigating the effects of diabetes by restoring glucose homoeostasis, flavonoids also control the secondary organ damage that occurs to different peripheral organs. In diabetic rats, hesperidin enhanced heart function and cured

 

neuropathic pain. In diabetic rats, chyrsin enhances cognitive function, delays the onset of diabetic neuropathy, and ameliorates renal disease. Peroxisome proliferator-activated receptor gamma (PPAR-γ) is a nuclear receptor found in macrophages and adipocytes. It modulates glucose metabolism and inflammation by upregulating transport proteins, fatty acid binding, adipokines, and the glucose transporter GLUT4. Moreover, it enhances lipid absorption, inulin sensitivity, and adipogenesis. Certain flavonoids, like luteolin, naringenin, and quercetin, alter the way PPAR-γ is activated and enhance insulin sensitivity. Furthermore, resistin, adiponectin, and leptin are only a few of the adipokines that are produced by PPAR-γ and are critical for preserving glucose homeostasis and reducing inflammation [8].

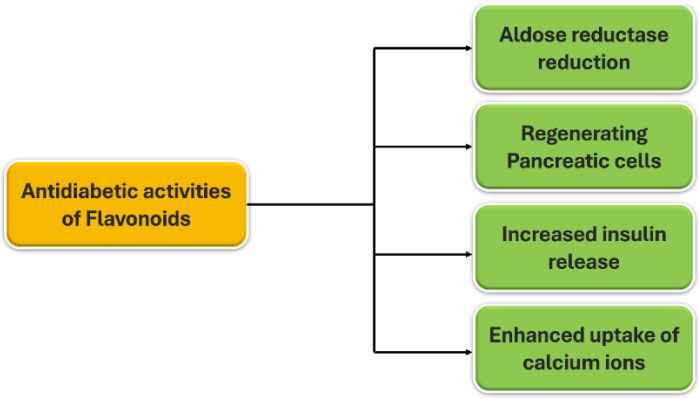


**Figure 1**. Antidiabetic activities of Flavonoids.

Adiponectin has been shown to prevent the release of cytokines including TNF-α and IL-6, which are known to cause inflammation. Lutein, which is abundant in fruits and vegetables like celery, parsley, carrots, and apple skins, increases the expression of PPAR-γ target genes, PPAR-γ transcriptional activity, adiponectin, leptin, and GLUT4 in 3T3-L1 adipocytes and primary mice adipose cells. It also potentiates the effect of insulin. Liu et al. suggest that luteolin could be the cause of the increase in adiponectin levels and decrease in the levels of circulating MCP-1 and resistin, two inflammatory molecules, in obese mice. Additionally, lutein has beneficial effects on metabolic pathways connected to the pathogenesis of insulin resistance.

**Potential role of Inflammatory Bowel Disease**

Inflammatory bowel disease (IBD) is a chronic disease characterized by Crohn's disease (CD) and ulcerative colitis (UC). Both conditions are marked by persistent gastrointestinal inflammation that alternates between remissions and relapses. The heightened uncontrolled intestinal inflammation that characterizes both types of IBD lowers quality of life and necessitates protracted medication and/or surgical procedures.

Intense gastrointestinal inflammation is found in patients suffering from inflammatory bowel disease (IBD). This inflammation is connected to intrinsic and adaptive immune responses, as well as impaired epithelial mucosal barrier function. Within inflammatory bowel disease (IBD), there are two primary clinical and pathological subgroups: Crohn's disease (CD) and ulcerative colitis (UC). Both forms of IBD lead to poor quality of life and require lengthy medical and/or surgical procedures. Even though CD can affect any part of the digestive tract, including the mouth and the anus, it usually affects the colon and/or the distal small bowel.

Conversely, UC is limited to the rectum and colon. Even though several theories have been proposed to explain the pathophysiology of IBD, the precise origin of the disease is still unknown. Patients with inflammatory bowel disease (IBD) who have higher tight junction permeability, and a defective

 

intestinal epithelial barrier experience an increased immune response in the gut that targets the intestinal microbiota. The pathophysiology of inflammatory bowel disease (IBD) has been shown to involve cytokines and chemokines, intestinal epithelial cells, innate immune cells such as dendritic cells, macrophages, and neutrophils, and cells of the adaptive immune system such as T cells and B cells. Since the etiology of IBD is unknown, there is no known treatment for the illness. Thus, flavonoids, which serve a multitude of biological purposes, could potentially aid in the treatment of inflammatory bowel disease. Flavonoids such as apigenin and epigallocathechin gallate have been shown to inhibit the activation of immune cells and the subsequent release of chemokines and cytokines; consequently, they can be considered as natural inhibitors that halt the activation of both the innate and adaptive immune systems. The anti-inflammatory properties of flavonoids have been widely reported in literature.

The various subclasses of flavonoids such as flavanols, flavones, isoflavones, chalcones, anthocyanidins flavanones and catechins have been shown to exhibit significant intestinal anti-inflammatory activity. Aglycones have been demonstrated to be more successful in lowering intestinal inflammation because they are digested in the colon and then released in the aglycone form, as opposed to being absorbed early in the intestines. Quercetin glycosides, like rutin and quercetrin, also have proved to be more potent against inflammation [9].

**Applications of Flavonoids in Cardiovascular Diseases**

Cardiovascular disease (CVD) is the leading cause of death and morbidity worldwide. Women who have cardiovascular disease are dying at a rate that has risen recently, surpassing the number of fatalities from breast cancer. Age and gender are the non-modifiable cardiovascular risk factors that are most frequently mentioned. Age-related increases in arterial stiffness and peripheral vascular resistance, in addition to a rise in plasma cholesterol, are the two main causes of the risk of cardiovascular events. Age determines the gender-related risk of cardiovascular disease (CVD), with men under 50 having a 3-5 times higher incidence of the disease than women. Above the age of 50, CVD occurs in women more significantly. Genetic factors, a sedentary lifestyle, obesity, smoking, high blood pressure, diabetes, and dyslipidemia are other risk factors that have been mentioned in the literature. Three mechanisms underlie the antioxidant effect of flavonoids: (1) the elimination of reactive oxygen species; (2) the prevention of reactive oxygen species production, which is secondary to the interaction of flavonoids with enzymes that regulate the production of free radicals; or (3) the enhancement of antioxidant system protection.

A single process or multiple mechanisms working together can produce the antioxidant effect. For instance, flavonoids can both directly remove and prevent the enzymes that cause reactive oxygen species to develop. Enzymes like Glutathione S-transferase, mitochondrial Succi oxidase, NADH oxidase, and microsomal monooxygenase are inhibited efficiently by flavonoids. Aglycones, which are hydroxylated flavonoids, can effectively block leukotriene formation, which impacts the latter stages of allergic reactions.

Because flavonoids protect against ischemic stroke by lowering blood pressure, oxidizing fat, and enhancing endothelial function, eating a diet high in them can lower the risk of having one. Furthermore, resveratrol administration has been shown to potentially decrease the volume of damaged tissue following ischemia in a study conducted on experimental models. This finding might be explained by a reduction in lipid oxidation. Polyphenols in grapes may decrease the amount of neurons ischemic damage [10].

## IMPROVEMENT OF BIOAVAILABILITY OF FLAVONOIDS

Since the 1930s, when it first started, the field of flavonoid study has expanded rapidly. Enhancing their bioavailability and comprehending their natural/synthetic availability were two of the most difficult tasks undertaken. Although flavonoids are not widely available, there have been new attempts to address this issue. There is recent data that suggests the gut and its microbiome are involved in the

 

production of phenolic compounds, which have prebiotic qualities and act as microbiota modulators. It is now evident that flavonoids reduce gastrointestinal inflammation, and their metabolites affect the immune system in the gut. Therefore, raising intestinal absorption of flavonoids is the primary goal of attempts to increase their bioavailability. From traditional medication absorption enhancers, such as the borneol/methanol combo, to intricate nano-delivery systems and even nano-antioxidant flavonoid carriers, research has progressed. Meanwhile, continuous advancements are also being made in the extraction of flavonoids. With all these developments, flavonoids will have increased bioavailability and beneficial impacts on human health [11].

## CONCLUSION

Numerous in-vitro, in-vivo, and epidemiological studies have shown that a broad range of flavonoids have anti-inflammatory qualities in several chronic inflammatory conditions, including diabetes, cancer, autoimmune diseases, cardiovascular disorders, and neurological diseases. Flavonoids are excellent lead candidates for the development of medicines because of their structural makeup and properties, which are clearly tied to their beneficial biological actions. Due to the presence of common phenol core, one of the most widely eaten flavonoids in everyday diets is apigenin, a flavone that also has anti-viral, antioxidant, and anti-cancer effects. Compared to other flavonoids in the same subclass, it is less toxic and does not cause mutations, which makes it a better option for development as a medicinal substance. Subsequently, a multitude of randomized clinical trials will be made possible by these studies, which will yield vital information about the drug's efficacy when used alone or in combination with other therapies to treat various chronic inflammatory disorders, including multiple sclerosis. There is a pressing need to provide safer, more natural therapeutic agents for the management and cure of chronic diseases because these conditions have crippling and destructive impacts on the patients. The limited bioavailability of a medicinal component derived from natural products is one of its biggest disadvantages.

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