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Review Article

Flavonoids: A Class of Polyphenols with Diverse Anti-inflammatory Activities and Mechanisms

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ABSTRACT

The impact of our dietary choices on our overall well-being is widely recognized in the field of nutrition. The influence of diet on human metabolism is widely recognized, by the consumption of an abundance of fresh fruits and vegetables being universally acknowledged as highly helpful. A number of ways have been proposed to understand the potential health advantages of incorporating fruits and vegetables into the food that one consumes. Right now, flavonoids have become prominent components in various products, such as nutritional and health foods, dietary supplements, and cosmetics as well. Glycosides are often encountered in nature, which include flavonoids. The complexity of flavonoids is made easier by the presence of sugar groups in their structure, which leads to their limited absorption over the gut wall. Flavonoid glycosides have the capacity of passing through the human digestive system and are thereafter metabolized in the colon by microbes that possess the capability to break down the glycosidic link. The above process promotes the production of flavonoid aglycones, which are then taken in by the distal end of the digestive system. Different experimental studies have shown the potential anti-inflammatory effects of flavonoid compounds. This review focuses on the influence of dietary flavonoids on signaling pathways related to inflammation, which subsequently impacts the formation of inflammatory mediators. The imperative involvement of flavonoids in preventing the growth of inflammation is highlighted to provide helpful perspectives.

Keywords: Flavonoids, Plant secondary metabolites, Inflammation.

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INTRODUCTION

Inflammation is the bodily response of live mammalian tissues to harm triggered by any external stimulus, leading to a localized reaction. It is an immune response that aims to destroy or contain a harmful substance, followed by the elimination of dead cells and tissues. This biological process includes the innate and adaptive immune systems. The patient experiences inflammation, which may appear in every part of the body. The symptoms of the disease include redness, pain, rash, burning, swelling, chronic soreness, and decreasing function. Recent findings indicate that the initiation of inflammation is a regulated and self-restricting mechanism of the immunological system.[1] The main purpose of inflammation is to resolve the infection, heal the damage, and restore the body to a state of equilibrium. The effectiveness of such a system relies on its capability to quickly respond to a specific type of inflammatory trigger while minimizing the harmful effects of inflammation. The best possible inflammatory response is characterized by its fast and destructive nature, when required, but also by being particular and self-limiting.[2]

Two types of inflammation that might take place are known as acute and chronic inflammation. During an acute inflammatory reaction, the body's defense mechanism acts in a unique way to combat harmful microbes or detritus effects from trauma. This response results in problems that are typical of acute inflammation, like redness, bruises, discomfort, and fever. During acute inflammation, however, the body increases the total number of white blood cells, commonly referred to as granulocytes, in the damaged tissue region. Following this procedure, a series of subsequent phases are carried out, each of which continues to affect the body's natural defense system before the damage or infection returns to its normal state of homeostasis. In most cases, the duration of this process is a few hours. Chronic inflammation is another form of inflammation that is characterized by a high level of inflammation that lasts for weeks or months. Whether it be genetically driven autoimmune disease processes or the presence of alien pathogens, chronic inflammation is caused mainly by the existence of external organisms as well as the continual generation of inflammatory modulators. There is an escalation in the biochemical indicators of inflammation that occur during chronic inflammation. This includes an excessive

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synthesis of Reactive Oxygen Species (ROS), which induces the presence of free radicals and increases inflammatory agents. These inflammatory cytokines include interleukin-17, interlukin-6, interlukin-4, and Interferon gamma (IFN-Y).[3]

Cyclooxygenase inhibition or cytokine receptor blockade are employed in most anti-inflammatory treatments. Consistent use of these medications causes side effects. Unsynchronized inflammatory responses increase inflammatory mediators, which can cause chronic illnesses that include cardiovascular disease, cancer, and rheumatoid arthritis. Inflammatory diseases may benefit from targeting inflammatory cytokines. Today, investigating flavonoids' effects on inflammatory mediators, specifically cytokines, is important to finding alternative treatments for inflammation-related ailments.[4]

Flavonoids, the most plentiful polyphenolic metabolites, are found in vegetation and the human diet and have cell-signaling and antioxidant advantages. These cover a wide range of water-soluble antioxidant compounds, such as anthocyanins, flavonols, flavones, and isoflavonoids (Figures 1 and 2). They are found in plants as glycosides and are formed by a pair of aromatic rings coupled by a carbon bond or a heteroaromatic ring. A few of these molecules have been identified in tea, red wine, and most fruits, herbs, and vegetables. Flavonoids can be found in a variety of foods, including green and black teas, beans, red wine, dry grains, and other beverages.[5,6]

Flavonoids possess the greatest significance in terms of nutrition. They are capable of a wide distribution in nature and may be found in both terrestrial and marine plant species or creatures. Flavonoids are a class of polyphenolic chemicals composed of 15 atomic carbons in the structure of two aromatic rings attached by a C3 bridge. The structural classification of these compounds encompasses several types of flavonoids, for instance, chalcones, flavan-3-ol, flavanols, flavonols, flavones, isoflavones and anthocyanins. Additionally, there are smaller groupings of compounds, including coumarins, aurones, dihydroflavones, and flavan-3,4-diols. These molecules are present in a wide variety of herbs, veggies, and fruits and may also be found in black tea, red wine, and, to a lesser extent, green tea. In addition to that, flavonoids may also be present in dietary sources such as beans and grains. Various surveys have been carried out to examine the anti-inflammatory properties of flavonoids and determine their effectiveness as therapeutic agents for treating inflammatory illnesses. Flavonoids work by inhibiting inflammatory mediators, including NO and ROS, as well as regulating the activity of inflammatory enzymes such as COXs and iNOS. Flavonoids significantly influence the function of transcription factors, such as Activating Protein-1 (AP-1) and Nuclear Factor-light chain-enhancer of activated B cells (NF-B).[7] They additionally produced a consequence for the production and release of cytokines. Recent research has demonstrated that flavonoids, including luteolin, apigenin, and quercetin, are capable of controlling the formation and release of cytokines.

This review emphasizes the function of flavonoids in the cure of inflammatory diseases. Numerous epidemic surveys have shown evidence that regular consumption of flavonoids reduces the possibility of cardiac arrests, hypertension, and mortality rates due to cardiovascular ailments.

Flavonoids in diet: Classification and Metabolism

Flavonoids, which are a kind of polyphenol, are the most prevalent in the human diet. They are characterized by a backbone structure consisting of six carbon atoms connected to the C6-C3-C6 backbone. Depending on their components, flavonoids can be divided into flavanones, flavones, flavanols, and flavonols.[8] They are abundant in nearly all of the plant-based foods and are particularly rich in citrus fruits, grapes, apples, berries, tea, onions, red wine, and olive oil. Quercetin, kaempferol, and myricetin are the most notable flavonols. Catechins are the dominant flavanols and are mostly found in tea leaves. The essential constituents of flavonones are taxifolin, naringenin, and hesperidin. Citrus fruits are the primary sources of flavanones. Flavones, including luteolin, wogonin, and apigenin, have been found in sweet red pepper and celery, but they are not as commonly found in these plants. Furthermore, cocoa products consist of other subclasses of flavonoids, including proanthocyanidins and their oligomers. The uptake of foods, including flavonoids, could vary depending on the dietary customs of distinct cultures. For example, soybean eating has historically been related to eastern civilizations, but tea drinking is more prevalent in provinces like Ireland, Turkey, the United Kingdom, and others.[9]

The colon plays a major role in the breakdown and absorption of flavonoids, as it breaks them down before they are transported to the liver for further breakdown. The liver produces metabolic substances that the body can transport to specific cells, recirculate through bile excretion, transform into aglycones by the microbiota, or eliminate from the body through feces or urine. The microorganisms in the colon possess the capacity to break down flavonoid metabolites that cannot find their way into the gut or reach the colon and thereafter absorb them over and over.[10]

Transport protein of flavonoids

Transport proteins can function as transporters, channels or pumps. Channels serve as specific routes for the rapid movement of particles flowing along an electrochemical gradient. Proteins within channels transport particles against their electrochemical gradient, consuming the cell's energy source, ATP. Transporters facilitate the movement of solutes across cell membranes without utilizing ATP hydrolysis.

There is still much to learn about membrane transporters pertaining to the absorption in the gastrointestinal tract and

distribution in tissues of flavonoids. Transporters typically have a broad substrate specificity, allowing them to transport both natural molecules and various drugs, including those not commonly found in nature.[11]

The transportation of flavonoids involves several types of transporters, including glucose transporters, monocarbohydrate transporters, organic ion transporters, and organic anion-transporting polypeptides.

Glucose is the predominant monosaccharide, which is included in the group of carbohydrates. SGLT1 and GLUT2 are transporters that have significant roles in the absorption of specific substances within the body. In Caco-2 cells, SGLT1 moves flavonoids like phlorizin around, and GLUT2 moves quercetin-3-glucoside around. SGLT1 and GLUT2 are transporters that are essential for the uptake of flavonoids and other compounds in the body. In the intestinal epithelium and basolateral membrane vesicles, they work to make it easier for these chemicals to move across cell membranes.[12]

Monocarboxylate transporters, often referred to as the Solate Carrier family 16 (SLC16), have an essential purpose in cellular metabolism and pH control. They have a crucial function in the transportation of gamma-hydroxybutyrate, a psychotropic medication, as well as other frequently prescribed drugs. Furthermore, organic anion transporters, also known as SLC22A family members, play a crucial act in the catalysis of membrane transporters for a array of exogenous and endogenous organic anions.[13] A solute-carrying organic anion transporter, or organic anion-transporting polypeptides, is last in the category. Particularly, the blood-brain barrier contains OATP1A2, OATP2B1, and OAT3 proteins. Additionally, they are found within the choroid plexus, an organ complex accountable for the synthesis of cerebrospinal fluid. Furthermore, placental and pulmonary tissues contain them. In general, they facilitated the independently absorbed sodium of an extensive variety of endogenous and exogenous substances, including pharmaceuticals.[14]

Bioavailability of flavonoids

Bioavailability refers to the rate and extent at which the active ingredient or active moiety is absorbed from a drug product and made accessible at the location where it has an effect. This similar approach may be used for flavonoid chemicals found in food. The effectiveness of a bioactive substance inside biological systems, or "bioavailability," is dependent upon its rate of absorption and availability at the site of action. Hence, it is crucial to ascertain the quantity of a particular nutrient or bioactive component present in a meal or dietary supplement, together with its bioavailability. While flavonoids have been associated with health benefits, the bioavailability of these compounds is not directly linked to the total amount of polyphenols utilized in the human diet. For flavonoids that have complex structures and higher molecular weights, their absorption may be further lowered.[15]

The bioavailability of the flavonoids that are altered depends on several parameters, including digestion, metabolism, and absorption. Researchers have found no direct relationship between the number of polyphenols found in the human diet and bioavailability. Enzymes like LPH, found in the epithelial cells of the gut, primarily absorb flavonoids through a process known as hydrolytic cleavage. LPH demonstrates a higher level of substrate selectivity in hydrolysing flavonoid O-D-glucosides. Through the process of passive diffusion, aglycone molecules can infiltrate epithelial cells. Furthermore, because of their increased lipophilicity, these molecules are comparable to the cellular membrane. In addition to this, a hydrolysis procedure takes place within the epithelial cells in the presence of CBG.[16]

Before entering the circulation, the aglycones undergo phase II metabolism, which involves the formation of glucuronide, sulfate and methylated metabolites. SULTs, COMTs, Uridine diphosphate and UDP-glucuronosyltransferase are enzymes that are responsible for carrying out this activity. Upon entering the circulation, metabolites quickly travel to the liver, where they may undergo additional phase II metabolism until their elimination.[17] Typically, intestinal enzymes do not break down flavonoid glycosides, leaving them unabsorbed in the small intestine. Inadequate absorption in the small intestine contributes significantly to the variation in flavonoid bioavailability. After consuming foods high in flavonoids, an examination reveals that the upper gastrointestinal tract absorbs the polyphenols present in the diet. The colon enzymes facilitate the passage of these polyphenols from the small intestine to the large intestine, where they break down the glycosides. Further decomposition of the aglycone molecules results in smaller compounds like hydroxycinnamates and phenolic acids, which the liver can readily absorb and process.[18,19]

Flavonoid detection and analysis in food sample

In recent years, the study of flavonoids in food has grown because they are considered bioactive substances with essential physiological effects on human health.[20,21] Various flavonoid analysis methods have been developed and improved, enhancing dietary flavonoid detection and characterization. However, the diversity of flavonoid-containing foods and biological sources necessitates a source-specific extraction and sample preparation method.

The extraction procedure is determined by the flavonoids-containing source; nevertheless, liquid extraction typically starts after the homogenization phase has been completed. Filtration and centrifugation are two more preparation methods that may be utilized. Cleanup comes after the extraction process. Frequently, High-Performance Liquid Chromatography (HPLC), Mass Spectrometry (MS), Nuclear Magnetic Resonance

(NMR), ultraviolet-visible spectroscopy and fluorescence, is required to successfully separate flavonoids from complicated biological extracts from one another. Nuclear magnetic resonance is useful for characterizing flavonoids in complex matrices; however, it is expensive and not suited for many applications. Mass spectrometry is presently the most popular approach for detection and characterization. Researchers have divided, identified, and determined flavonoids using Ultra-High-Pressure Liquid Chromatography (UHPLC) and mass spectroscopy.

Anti-inflammatory impacts of flavonoids: Action mechanism

By inhibiting regulatory enzymes and transcription factors, flavonoids can exert their anti-inflammatory properties. These enzymes and transcription factors play an essential part in the regulation of the mediators that are associated with inflammation. Flavonoids are extremely potent antioxidants that have the potential of eliminating free radicals and inhibit the frequency with which they are produced. There are a number of immune cells and immunological pathways that are highly influenced by flavonoids, and these pathways play a significant part in the processes that cause inflammation. The main approach through which dietary flavonoids and related polyphenols exert their effects is through the inhibition of regulatory enzymes, effect on arachidonic acid metabolism, and alteration of gene expression and immune cells. Flavonoids not only reduce the activity of signal transduction and cell activation, but they also limit the release of pro-inflammatory substances such prostaglandins, thromboxanes, leukotrienes, etc. Furthermore, flavonoids suppress the activation of genes that promote inflammation and impede cell growth.

Suppression of protein kinases and transcription factors

Protein kinases transferred to phosphate groups from high-energy donor molecules like ATP to substrates. This is known as phosphorylation. Phosphorylation of these regions in target proteins activates signal transduction pathways that affect cell growth, biological activities, development, differentiation, and death. The enzyme that triggers cells in inflammation via signal transduction. Some flavonoids can directly bind to protein kinases connected to cellular signaling cascades and change their catalytic activity influencing various signaling pathways. Flavonoids hinder the activity of kinases such as protein kinase C, also known as tyrosine, phosphatidylinositol, phosphoinositol and cyclin dependent kinase-4.[22]

It has been proven that flavonoids are responsible for managing the activity of both IκB and NF-κB and this regulation has immediate effects on the stimulation of cells. Moreover, flavonoids have the capacity to modify protein kinases by inhibiting transcription factors including NF-κB. The transcription factor in concern is accountable for the regulation of cell adhesion molecules, chemokines and inflammatory cytokines overall. During inflammation, IκB, a molecule that functions as an inhibitor of NF-B, undergoes phosphorylation and degradation. Because of this, the Nuclear Factor kappa B (NF-κB) moves from the cytoplasm to the nucleus. This causes the transcription of several genes related to inflammation.[23] Furthermore, flavonoids can change the main transcription factors that control CD4+T helper 2 (Th2) cytokines. These transcription factors include GATA-3, activator of transcription 6 and signal transducer.[24]

Inhibition of phosphodiesterase

Flavonoids can impact the function of phosphodiesterases, such as cAMP phosphodiesterase. cAMP is a crucial secondary messenger that exerts significant influence over various cellular processes involved in the development of inflammation. Increased levels of cyclic adenosine monophosphate have been connected to the promotion of anti-inflammatory effects. Phosphodiesterases have the capacity to break down cAMP, which helps to keep its levels within the normal range. Flavonoids possess the remarkable capability to hinder certain processes, thereby protecting the integrity of cAMP and extending the signaling of cAMP phosphodiesterases.[25]

Anti-oxidant activity

Inflammation leads to tissue damage, which is found in the production of free radicals. These free radicals, which contain reactive oxygen forms and reactive nitrogen types, are two names for radicals that come from oxygen and nitrogen and, accordingly, are known to have negative effects on the function of cells. A review that was conducted barely a decade ago provides proof that the mechanism of action of flavonoids in lotus plumule was extensively examined by employing radical scavenging tests and ELISA kits.[26]

Flavonoids, through their ability to donate electrons and H atoms, as well as their ability to capture DPPH and ABTS+ free radicals, exhibited a remarkable antioxidant activity. Furthermore, flavonoids exhibited anti-inflammatory effects by inhibiting the formation of inflammatory mediators, namely NO radicals, PGF2, and TNF-α, as well as cytokines that cause inflammation, such as IL-1β and IL-6. The fact that free radicals possess electrons that are not coupled with other electrons makes them very reactive and harmful to DNA, lipids and proteins. The effects of free radicals on cellular membranes, that occur as an outcome of the process of lipid peroxidation, as well as the effects of free radicals on proteins and nucleic acids, and this occur after oxidative damage. The development of oxidative stress is brought about by a confluence of factors, including a high generation of free radicals, a poor separation of transition metal ions, and a down activity of free radical scavenging. These variables all influence the presence of free radical damage.[27]

Impact on arachidonic acid pathway

Whenever inflammation is occurring, the enzyme known as Phospholipase A2 (PLA2) is responsible for the elimination of arachidonic acid from the phospholipids that are found in the plasma membranes. The subsequent step involves the metabolization of arachidonic acid by several oxygenase's, including Lipoxygenase (LOX) and Cyclooxygenase (COX), which results in the production of prostaglandins, thromboxanes, leukotrienes, and other inflammatory mediators. Flavonoids have the capacity to suppress the activity of enzymes that relate to the metabolism of arachidonic acid. As a result, flavonoids can reduce the formation of inflammatory mediators that are generated along this route. For example, flavonoids have the potential to limit the formation of thromboxanes, prostaglandins and leukotrienes by inhibiting the enzymes PLA2, COX or LOX.[28]

Impact on immune cells

Flavonoids influence the activity, maturation, signaling transduction, production, and secretion of immune cells. Flavonoids lower the levels of development markers such as CD80 and CD86, which are essential for CD4+ T cell activation, while enhancing dendritic cell maturation. This would result in cytokine production and CD4+ T cell proliferation.[29] Flavonoids modulate iron metabolism and DC inflammatory response. Flavonoids can reduce mast cell histamine or prostaglandin secretion or mast cell, neutrophil, and other immune cell pro-inflammatory cytokines or chemokines, according to several studies. Flavonoids can inhibit cell signaling by binding to inflammatory meditators like the IL-17RA element of the receptor. Flavonoids suppress downstream signaling from many receptors, including the FcεRI, at the site of inflammation.[30] Flavonoids can limit monocyte adhesion or reduce immune cell activation and proliferation involved in chronic inflammation.[31]

Role of flavonoid phytoconstituents in the management of inflammatory disease

Apigenin

Apigenin is labeled as 4',5,7-trihydroxy flavone in the chemical formula. For example, parsley, onions, and celery all have a significant amount of it. Apigenin possesses a number of health benefits, along with anti-inflammatory, anti-oxidant, and anti-cancer actions. As a consequence of this, apigenin has garnered a great deal of interest over the course of the past several years as a therapeutic active ingredient suitable for the therapy of a variety of disorders, like cardiovascular disease, diabetes, cancer and neurodegenerative diseases.

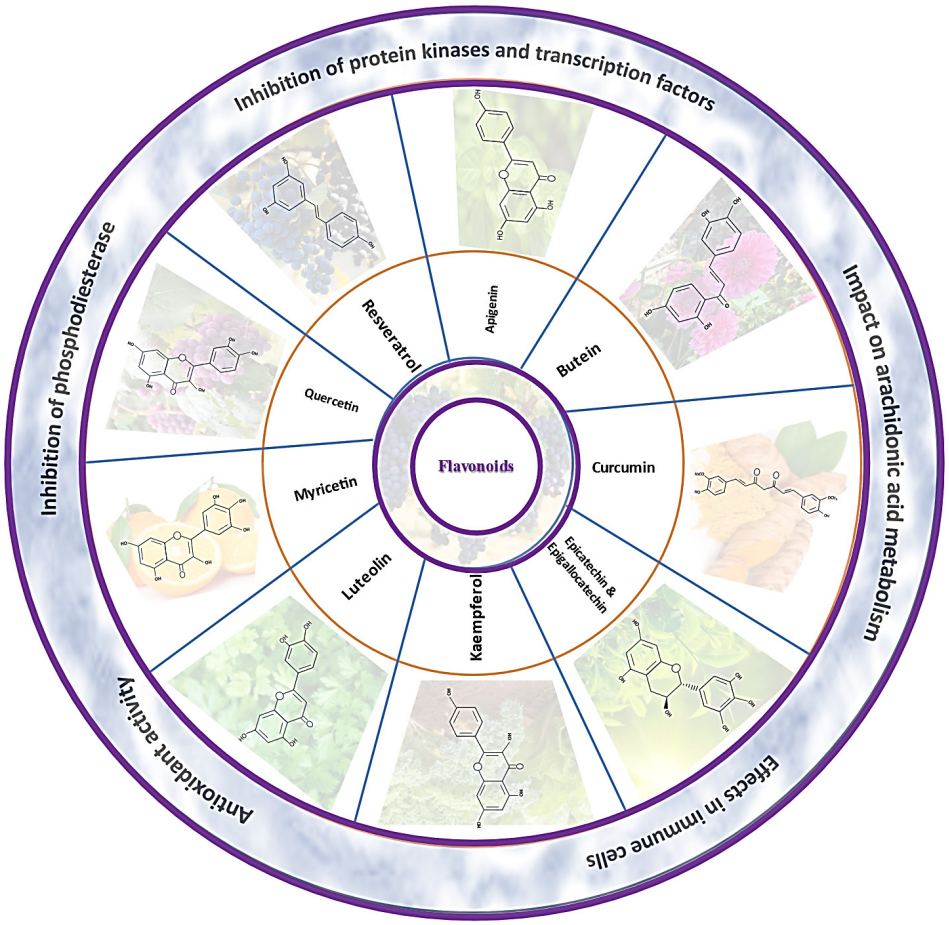

Figure 1: Basic chemical structure of different flavonoids.

When mouse macrophages and human monocytes are activated by Lipopolysaccharide (LPS), apigenin can reduce the amount of TNF-alpha and IL-1β in these cells.[32] Apigenin inhibits the synthesis of prostaglandin-endoperoxide synthase-2 and nitric oxide synthase in mice macrophages that have been activated by Lipopolysaccharide (LPS), which results in a reduction in inflammation. It does this by inhibiting the activity of NF-kappa B, which is responsible for the suppression of inflammatory reactions. Through its ability to prevent neutrophils and lymphocytes from adhering to endothelial cells, apigenin possesses the capacity to mitigate the inflammation that occurs. The regulation of the expression of ICAM and VCAM is another mechanism that contributes to the adhesion of monocytes to HUVECs.[33,34] Additionally, apigenin is able to reduce the inflammation of the airways that is caused by allergens. Based on the results of this investigation, it appears that various intracellular signaling pathways, including NF-B, MAPK/ERK, and JNK, regulate the anti-inflammatory qualities of apigenin.[35,36] Apigenin was able to reduce the generation of IL-1β that was produced by LPS. By interfering with the proliferation of the NLRP3 inflammasome in human macrophages that THP-1 had triggered, we were able to reduce the activation of caspase-1. This prevented TNF- and IL-1 from activating NF-B. In addition to this, it prevented the formation of AP-1 proteins and the development of proinflammatory cytokines, including NO, iNOS, and COX-2. The findings demonstrate that apigenin reduces inflammatory mediators and AP-1 factors. Studies have shown that apigenin can treat lung inflammation.[37,38]

Butein

Butein is another form of plant polyphenol known as 2',3,4,4'-2',4',3,4- or 3,4,2',4'-tetrahydroxychalcone. It was extracted from the leaves of *Viburnum propinquum* Hemsl., the blooms of *Coreopsis douglasii* HM Hall, *Toxicodendron vernicifluum* (Stokes) FA Barkley's stem bark the heartwood of *Cotinuscoggygria* Scop, and several other species It has been declared to demonstrate many pharmacological actions against inflammation and cancer and also have anti-angiogenic and anti-oxidant aspects. Butein is a compound that is formed by the combination of two benzene rings that are connected by a double bond and an a,b-unsaturated carbonyl group.[39]

The study investigated the anti-inflammatory therapeutic impact of butein in RAW 264.7 macrophages by stimulating the enzyme Heme Oxygenase-1 (HO-1). Through the utilization of the HO-1 small interfering siRNA technology, the effectiveness of the zinc protoporphyrin (ZnPP) treatment, which is a particular inhibitor of HO-1, was further verified. Consistent with the above findings, butein revealed greater inhibitory effects on the activity of the NFjB reporter gene and the migration of Nuclear Factor jB (NFjB) in lipopolysaccharide-activated macrophages. Butein may reduce NF-jB levels and prevent NF-jB activation in human mast cells, resulting in a reduction in the production of TNF-α, IL-6, and IL-8. Butein has the multiple potential of reducing NF-jB levels and inhibiting NF-jB activation in human mast cells. This ultimately culminates in a drop in the release of IL-6, IL-8 and TNF-alpha. When it comes to adipocytes, it also inhibits IKKb, which is an upstream kinase of NF-jB.[40,41] Furthermore, with regard to lung epithelial A549 cells, it has anti-inflammatory property by inhibiting the development of free radicals that are generated by TNF-α. Additionally, it reduces the stimulation of NF-jB, the phosphorylation of MAPK, and the phosphorylation of Akt. Furthermore, it decreases the adhesion of monocyte cells to lung epithelial cells, which is a phenomenon that is triggered by TNF-α. It is also effective in treating inflammatory bowel diseases by lowering the production of Interferon (IFN)-c, interleukin-6, interleukin-1b, and Matrix Metalloproteinase-9 (MMP-9) in mice that are deficient in IL-10.[42]

Curcumin

Curcumin is an element that comes from the dried rhizome of turmeric, *Curcuma longa* Linn., which is a member of the Zingiberaceae family. This substance is a widely used anti-inflammatory medication that has demonstrated strong effectiveness in treating several chronic inflammatory conditions, including bowel inflammation, cognitive impairment, rheumatoid arthritis, and potential malignancies such as breast, lung, colon, stomach, and skin cancers.[43]

Curcumin reduces inflammation by blocking the action of COX enzymes (COX-1 and COX-2), which prevents the impeding of the synthesis of PGE2, eicosanoids, and 5-hydroxyeicosatetraenoic acid. Curcumin inhibits the synthesis of COX-2, NF-kappa, lipoxygenase, NO, and iNOS in macrophages and NK cells that have been stimulated by TNF-α or LP, hence preventing inflammation-related reactions.[44] Curcumin can inhibit the activity of AP-1 in bovine aortic endothelial cells that have been activated by TNF. In splenic lymphocytes, dendritic cells, and macrophages that have been triggered by Lipopolysaccharide (LPS), it suppresses the accumulation of Interferon-gamma (IFN-γ) and cytokines that are responsible for inflammation.[45] Curcumin has been demonstrated to effectively decrease the release of alveolar macrophages, IL-1b, IL-8, MIP-1a, MCP-1 and LPS-stimulated monocytes. In a human myelomonoblastic cell line, it has been demonstrated that curcumin can inhibit the activation of NF-kappa B, which is activated by either TNF-α or hydrogen peroxide. Through the process of inhibiting the degradation and phosphorylation of IkBα, this inhibition is achieved. Curcumin may impact the expression of genes involved in inflammation by suppressing the activity of transcription factors, which include AP-1, NF-kB, PPAR-g, and STAT proteins. Cell adhesion molecules play an important role in the process of inflammation, which enables T lymphocytes to attach themselves to antigen-presenting cells and endothelial cells involved in the process. Curcumin administration prior to treatment showed in the inhibition of monocyte attachment to endothelial cells,

as well as a decrease in the expression of vascular cell adhesion molecule-1, intracellular adhesion molecule-1, and Endothelial Leukocyte Adhesion Molecule (ELAM). The approach that was utilized for achieving this conclusion involved inhibiting the activation of NF-kappa B in Human Umbilical Vein Endothelial Cells (HUVEC) upon stimulation with TNF.[46]

Epicatechin and Epigallocatechin

Epicatechin (EC) and Epigallocatechin Gallate (EGCG) are prominent proanthocyanidins derived from polyphenols. These compounds are found in high concentrations in *Camellia sinesis* leaves, which are widely consumed worldwide. In addition, berries and commonly eaten fruits such as grapes and berries include EC and EGCG in lower amounts, whereas catechins, chocolates, and non-alcoholic drinks have the highest concentrations of these compounds. Several *in vitro* and *in vivo* investigations conducted on different types of tissues have substantiated the anti-inflammatory effects of ()-epicatechin, as it mitigates the reactivation of the NF-B signaling pathway.[47,48]

Epicatechin can significantly improve many factors related to inflammation of visceral adipose tissue fat in mice on a high-fat foods. Epicatechin was discovered to inhibit the infiltration of adipose macrophages, as shown by decreased levels of NOX2 protein and F4/80. Additionally, it activates proinflammatory signals through NF-kB and decreases the levels of chemokines like MCP-1 and cytokines (TNF-α) in tissues. The intake of epicatechin has been proven to decrease the release of pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6) as well as the Production of Inflammatory Cytokines (PGE2), as well as the function of cyclooxygenase-2 and inducible nitric oxide synthase in RAW264.7 cells that have been stimulated by Lipopolysaccharide (LPS). The process involves sequential movement of NF-κB p50/P65 subunits and inhibition of κB kinase α/β activation. Epicatechin has the potential to enhance the ability of visceral adipose tissue to respond to insulin and decrease inflammation by reducing oxidative stress and the activity of adipocyte endoplasmic reticulum.[49,50] Epicatechin might potentially reduce inflammation and enhance insulin sensitivity in visceral adipose tissue by inhibiting oxidative stress and adipocyte endoplasmic reticulum. Furthermore, several research studies have demonstrated that EGCG has the ability to reduce inflammation in both humans and animals, hence decreasing the risk of oxidative stress, diabetes, arthritis, and the production of inflammatory mediators. In addition, scientists have shown that EGCG activates AMPK to inhibit inflammation in immune cells. Using an experiment, it was shown that activation of AMPK may inhibit the synthesis of a variety of proinflammatory mediators. The generation of nitric oxide and Prostaglandin E2 (PGE2) by murine RAW 264.7 macrophages that had been stimulated with Lipopolysaccharide (LPS) was considerably lowered in the presence of EGCG-DPA esters. The main reason for this inhibition was the decrease in transcription of the iNOS and COX-2 genes.[51,52]

Kaempferol

Kaempferol is a flavonoid compound with a chemical structure of 3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one. It is usually known as kaempferol-3, kaempferide, or kaempferol flavonol. Kaempferol has hydrophobic characteristics as a result of the existence of a diphenyl propane framework. It may be extracted from several common vegetables and fruits, such as broccoli, beans, cabbage, grapes, citrus fruit, kale, tomatoes, apples, and so on. Kaempferol has been shown to have positive benefits on chronic inflammatory conditions such as intervertebral disc degeneration, post-menopausal bone loss, and colitis. One of the key attributes of kaempferol is its ability to inhibit the development of cancer. Kaempferol has the ability to hinder inflammation in the blood vessels, maintain the heart's function, safeguard the cranial nerve, and address fibroproliferative illnesses.

Activation of nuclear factor kappa B has been found to be regulated by the giving of kaempferol by injection. The release of additional pro-inflammatory chemokines, cytokines, and enzymes is an outcome of this. They include IL-1, IL-6, IL-8, iNOS, COX-2, and TNF-α. Additionally, kaempferol suppresses the activity of NF-B. The administration of kaempferol demonstrates the suppression of COX enzymes.[53] Kaempferol effectively suppresses the generation on nitric oxide production by RAW 264.7 macrophages treated with LPS. In macrophages derived from human promonocytic U937 cells (dU937), the secretion of TNF-α, IL-8, and macrophage inflammatory protein 1 alpha (MIP-1α) decreased significantly while delivered at dosages of 25 and 50 μmol/L of kaempferol. Lipoxygenase (LOX) plays a significant part in the process of converting Arachidonic Acid (AA) into leukotrienes. This pathway is closely linked to the development of certain inflammatory conditions, such as rheumatism, inflammatory bowel disorder, and asthmatic symptoms. Kaempferol has demonstrated inhibitory effects on the activity of LOX, decreasing the production of NO induced by LPS in J774 cells and RAW264.7 cells, and mitigating the overall inflammatory response.[54] Kaempferol mitigates inflammation and allergic reactions induced by anti-IgE in cultured mast cells obtained from human umbilical cord blood. This is achieved by suppressing the synthesis of proinflammatory cytokines. Kaempferol effectively reduced the inflammation caused by LPS in airway epithelial cells by blocking the Tyk-STAT signaling pathway. It successfully suppresses inflammation in the airways of human airway epithelial BEAS-2B cells and minimizes allergy reactions produced by ovalbumin in BALB/c mice. The main method it reduces inflammation in cardiac fibroblasts is by suppressing the NF-B signaling pathways. Administering kaempferol to murine microglial BV2 cells and synovial fibroblast cells obtained from those suffering from rheumatoid arthritis leads to a substantial decline in their production of Nitric Oxide (NO), Prostaglandin E2 (PGE2), and the enzymatic activity of Inducible Nitric Oxide

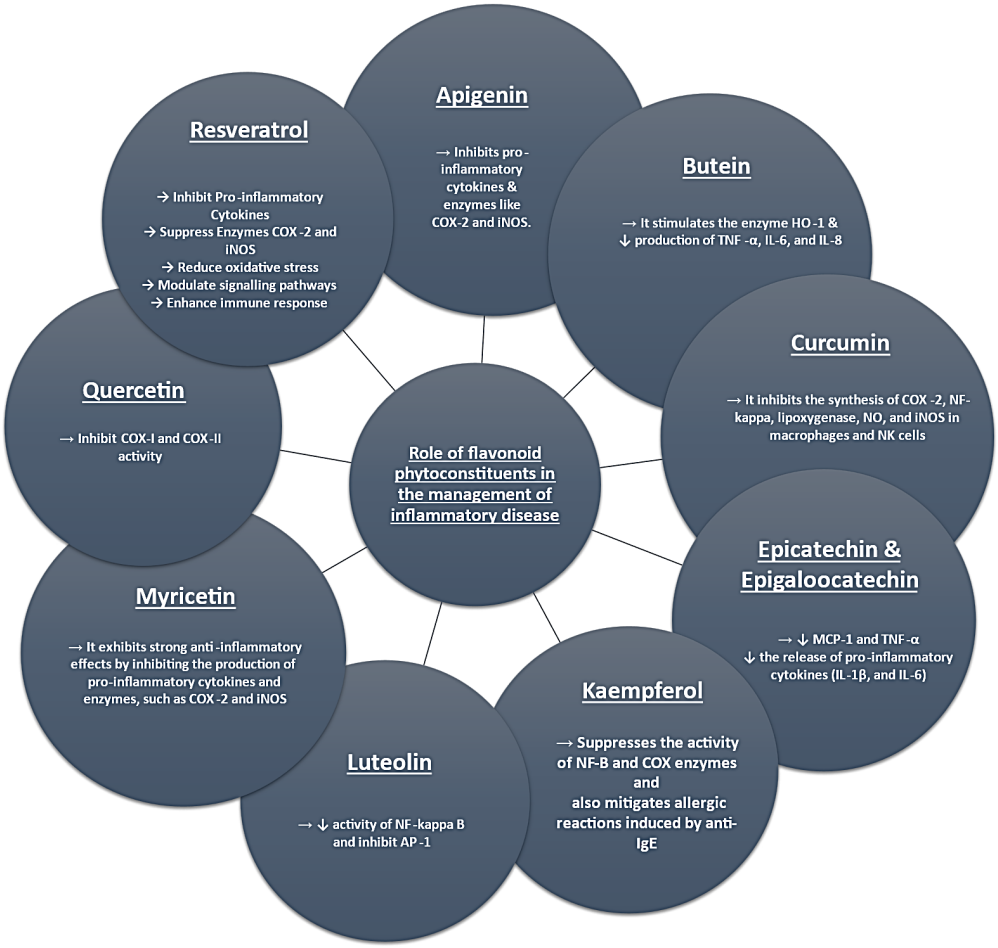

Figure 2: Role of flavonoid phytoconstituents in the management of inflammatory disease.

Synthase (iNOS).[55] One study that revealed a substantial decrease in the production of MMP in rheumatoid arthritis synovial fibroblast cells when supplemented with kaempferol. Conversely, treating IL-1 resulted in an increase in MMP expression. At doses of 25 and 50 μmol/L, kaempferol considerably reduced the formation of TNF-α, IL-8, and Macrophage Inflammatory Protein 1 alpha (MIP-1α) in macrophages produced by human promonocytic U937 cells (dU937).[56]

Luteolin

Numerous kinds of novel anti-inflammatory substances may be discovered in several phytochemicals produced by food and their derivatives. Luteolin, widely referred to as 3,4,5,7-tetrahydroxy flavone, is present in various plants, such as vegetables, fruits, and medicinal plants. Some examples of plants that contain luteolin are carrots, broccoli, onion leaves, cabbage, peppers, and apple skins. *Ocimum basilicum, Apium graveolens, Cynara cardunculus* var. scolymus, *Thymus vulgaris, Petroselinum crispum*, and *Mentha piperita* Linn. have been shown to have a significant amount of luteolin. Additionally, due to its anti-inflammatory characteristics, luteolin has been shown to possess antioxidant, antimicrobial, antidiabetic, antiallergic, chemo preventive, neuroprotective, cardioprotective, and chemotherapeutic activities.[57]

Luteolin's biological actions may be attributed to its actions to modulate levels of reactive oxygen species, reduce activity of NF-kappa B, and inhibit AP-1. Luteolin exerts inhibitory effects on the generation of nitric oxide, the function of inducible nitric oxide synthase and the expression of iNOS. According to reports, luteolin acts as a scavenger of reactive oxygen species, inhibits the generation of ROS, and activates antioxidant enzymes. Due to the labile nature of NO, luteolin's capacity to control ROS is associated with this inhibition. Both *in vitro* and *in vivo* investigations prove luteolin's anti-inflammatory actions.[58] An experiment was conducted where *Chrysanthemum indicum* was extracted using methanol. The results showed that this extraction method was able to reduce the inflammatory response in macrophages. Besides that, luteolin stops several pro-inflammatory cytokines from working. These include granulocyte-macrophage colony-stimulating factor, IL-1β, IL-2, IL-6, IL-8, IL-12, IL-17, TNF-α, and Interferon (IFN-β). Furthermore, it could elevate the levels of the cytokine that suppresses inflammation, IL-10.[59] *In vitro* investigations have demonstrated that the ethyl acetate partition of *Vernonia condensate*, also known as Figatil, effectively decreased the levels

of anti-inflammatory mediators, specifically IL-6 and TNF-alpha, at doses of 5, 10, and 20 μg/mL.[60] Nevertheless, the application of topical treatments using an infusion of *Cymbopogon citratus* leaves, commonly referred to as lemongrass, demonstrated anti-inflammatory effects in carrageenan induced rat pae edema. These effects were observed with both 4% and 1% w/w extracts.[61] Several studies have demonstrated that luteolin has the ability to decrease IL-6 production generated by LPS both in laboratory settings (*in vitro*) and in living organisms (*in vivo*) via blocking the JNK and AP-1 signaling pathways. Researchers discovered that mice given luteolin in their drinking water saw a decrease in IL-6 levels in their blood plasma and a reduction in IL-6 production in the hippocampus. Luteolin's anti-inflammatory benefits are likely a result of its inhibitory effects on pro-inflammatory enzymes.[62]

Myricetin

Myricetin is a naturally-occurring polyhydroxy-flavonol molecule that has hydroxy substitutions at positions 3, 5, 7, 3', 4', and 5'. It is mostly ingested in our diet through the consumption of fruits, vegetables, berries, and drinks like tea and wine. The presence of this substance is prevalent in several plant families, such as Myricaceae, Leguminosae, Vitaceae, Rosaceae, Ericaceae, Compositae, and Fagaceae. The presence of myricetin in fruits, vegetables, and berries is mostly in the form of glycosides rather than free aglycones. Furthermore, the concentration of myricetin in berries significantly rises as they mature. Recent pharmacological studies have demonstrated that myricetin exhibits a diverse range of activities, including anti-inflammatory, anti-viral, anti-obesity, anti-tumor and anti-bacterial effects. It also provides protection against neurological damage, exerts cardiovascular benefits, and safeguards the liver from potential injuries. COX-I is widely distributed in many bodily tissues, while COX-II is specifically overexpressed at the site of inflammation. Inhibiting or obstructing the activity of COX-I and COX-II can indicate pain-relieving, fever-reducing and inflammatory properties. The inhibition of Cyclooxygenase-1 (COX-I) by myricetin suggests its potential as an anti-inflammatory agent. The structure-activity correlation indicates that the high inhibitory effect on COX-2 synthesis is largely due to the presence of a double bond at C2-C3 and a keto group at C-4.

Myricetin has beneficial anti-inflammatory properties by inhibiting IκBα degradation, blocking the translocation of the p65 protein responsible for NF-κB synthesis, and lowering the DNA binding activity of NF-κB in RAW264.7 macrophages stimulated by Lipopolysaccharide (LPS). Additionally, myricetin induced the movement of Nrf2 to a new location inside the cell, which resulted in the stimulation of the synthesis of HO-1. It has been shown that myricetin can inhibit the release of proinflammatory chemicals by inhibiting the activation of NF-κB and STAT1 and by boosting the expression of Nrf2-mediated HO-1 in RAW264.7 macrophages that have been primed with Lipopolysaccharide (LPS).[63]

Based on the evidence provided, it appears myricetin has the capacity to serve as a strong anti-inflammatory drug, with the capability to treat plenty of conditions that are inflammatory. According to the results of a study that was conducted with JB6 P+ mouse epidermal cells, the activation of NF-B may be successfully inhibited by Myricetin at doses anywhere between 10 and 20 M. This inhibition leads to a reduction in phorbol ester-induced COX-2 synthesis. Further, it inhibited the DNA binding activity of NF-B that was stimulated by phorbol ester and it also reduced the production of PGE2 induced by phorbol ester.[64] Myricetin demonstrates efficacy against periodontitis, an infectious inflammatory condition resulting from the presence of bacteria in dental plaque that affects supporting bone and the connective tissue surrounding the teeth. Myricetin, at doses ranging from 62.5 to 125 g/mL, shown effectiveness for decreasing the inflammatory response caused by the growth of Porphyromonas gingivalis in host cells. Furthermore, it inhibited the activation of NF-κB in a monocyte model. Additionally, this molecule suppresses the release of IL-6, IL-8, and MMP-3 by gingival fibroblasts that have been activated by *P. gingivalis*. Periodontitis is a harmful gum infection that causes damage to soft tissue and tooth bones. The study suggested the potential use of myricetin as a medicinal treatment for periodontitis.[65]

Quercetin

Quercetin is a ubiquitous polyphenolic bioflavonoid pigment that is rich in apples, onions, teas, and green vegetables. For ages, it has been a staple in human diets. It has several health advantages, including anti-inflammatory, antioxidant, antimicrobial, antiviral, and anticancer properties. Quercetin's anti-inflammatory effects are achieved by blocking the synthesis of enzymes that cause inflammation, which makes it a promising treatment for several inflammatory conditions.

Quercetin is recognized for its potent anti-inflammatory properties. Numerous *in vitro* studies using various cell types have shown that quercetin effectively reduces the generation of tumor necrosis factor induced by lipopolysaccharide in macrophages, as well as the production of IL-8 developed from LPS in lung A549 cells.[66] It reduces LPS-induced inflammation by blocking the phosphorylation of Phosphatidylinositol-3-Kinase (PI3K) -(p85) through the regulation of Src and Syk. This prevents the development of the Toll-like Receptor 4 complex, thereby inhibiting the start of subsequent signaling cascades in RAW 264.7 cells.[67]

In addition, it can block FcRI, which is participating in the synthesis of pro-inflammatory cytokines, histamine and tryptase from cultured mast cells that are derived from Human Umbilical Cord Blood (hCBMCs). It appears that the reduction of calcium influx and phospho-Protein Kinase C (PKC) is

connected to this inhibition.[68] The research study examines any potential anti-inflammatory properties of quercetin against the inflammatory response induced by Hydrogen Peroxide (H_2O_2) in Human Umbilical Vein Endothelial Cells (HUVECs). This effect was mediated by CD80 expression and VCAM-1 downregulation.[69]

Quercetin revealed the ability to inhibit the signaling processes of NF-kappa B, STAT-1, and AP-1 in HUVECs and cytokine-stimulated macrophages. The inhibition causes a reduction in iNOS and COX-2 activity. This discovery was made by scientists.[70]

Quercetin was found to have powerful inhibitory effects on the formation of adhesion molecules in human endothelial cells when they were exposed to kaempferol. These adhesion molecules included VCAM, ICAM-1, and E-selectin to name a few. In mast cells that had been stimulated by PMA and Calcium Ionophore (PMACI), the levels of proinflammatory cytokines were decreased by the presence of quercetin. The drug further decreased NF-kappa B recruitment to inflammatory substances gene promoters in TNF-induced mouse intestinal epithelial cells.[71] Research conducted in recent times has demonstrated that quercetin has the ability to limit the production of proinflammatory cytokines by exerting an influence on NF-κB and p38 MAPK in a particular kind of human mast cell.[72] Quercetin with its ability to increase the levels of PPARα, effectively decreased inflammation in cutaneous eczema. This was accomplished principally by a significant reduction in the quantities of cytokines that are responsible for inducing inflammation. It has been observed that the activity of the NF-κB/cAMP-induced element binding protein/AP-1 signaling pathway in murine macrophages is considerably reduced by the presence of quercetin.[73] Furthermore, it has been found that quercetin not only inhibits the formation of proinflammatory cytokines but also boosts the levels of IL-10 in mice that had LPS-induced inflammation initially present.[74] Other studies suggest that the consumption of quercetin in CIA C57BL/6 mice results in anti-inflammatory and protective advantages. A correlation exists between the decline in the amounts of TNF-α, IL-1β, IL-17, and MCP-1 and the observed beneficial effects.[75]

Resveratrol

The stilbene family is a group of naturally occurring polyphenols, and resveratrol, commonly referred to as 3,4',5-trihydroxy stilbene, is one of them. Researchers propose that dietary resveratrol may possess the ability to perform a variety of roles, including those of an antioxidant, anti-inflammatory, platelet inhibition, anti-hyperlipidemic, anti-carcinogenic, immune-modulator, vasorelaxant, cardioprotective, and neuroprotective agent. Grapes, berries, and nuts represent just some of the meals and foods that contain resveratrol. Resveratrol may also be present in human diets. When seen from a botanical standpoint, resveratrol has the characteristics of a phytoalexin, which is a poisonous substance that plants create in reaction to an attack by a parasite.[76]

Laboratory research, done both in living organisms (*in vivo*) and in controlled environments (*in vitro*), show multiple proofs that preventing the production of substances that reduce inflammation may account for the anti-inflammatory qualities of resveratrol. The inquiries have been carried out on both animal and human participants. Researchers have discovered the use of resveratrol as an example. Different kinds of Pattern Recognition Receptors (PRRs), such as Toll-Like Receptors (TLRs), have the potential to identify both Pathogen-Associated Molecular Patterns (PAMPs) and Damage-Associated Molecular Patterns (DAMPs). Activation of the PRR triggers the beginning of intracellular signaling cascades, which encompass kinases, transcription factors, and other mediators. The signaling pathways mentioned earlier can activate the synthesis of several inflammatory mediators including cytokines, which are crucial for the advancement of inflammation.[77]

Based on current research, these signaling pathways prevent spleen cell proliferation triggered by ConA, IL-2, or allo-antigens. They further inhibit lymphocyte and macrophage IL-2, IFN-, and TNF-/IL-12 release.[78] Resveratrol has been shown through laboratory experiments to successfully lower the stage of IL-1, IL-6, and TNF in a manner that depends on the dosage. Additionally, it has a tendency to decrease both the production of IL-17's mRNA and the release of its protein.[79] As a living organism, exposure to of resveratrol by meals can enhance the production of certain proteins that are responsible for maintaining the integrity of tight junctions, including zonula occludens-1, occludens-1, and claudin-1. As a result, this leads to a reduction in the permeability of the intestines.[80,81] Resveratrol treatment led to a lowering of the expression of inflammatory factors such as Glycation end Product Receptor (RAGE), NF-κB (P65), and Nicotinamide Adenine Dinucleotide Phosphate (NADPH) Oxidase 4 (NOX4) and also maintained the structure of the kidneys.[82] Also, polydatin, a glycoside of resveratrol obtained from *Polygonum cuspidatum*, substantially lowered the formation of IL-6, IL-1, and TNF in *Mycoplasma gallisepticum* in both *in vivo* and *in vitro* environments. This shows that polydatin exhibits anti-inflammatory effects.[83] Resveratrol may exert anti-inflammatory effects by minimizing the buildup of reactive oxygen species and nitric oxide. Oxidative stress, caused by the accumulation of reactive oxygen species, induces inflammation in several conditions, including chronic inflammation and cancer.[84] Experts have shown that resveratrol has a potent capacity to prevent the formation of Nitric Oxide (NO) in activated macrophages. It also significantly reduced the concentrations of cytosolic Inducible Nitric Oxide Synthase (iNOS) protein and steady-state mRNA. Supplementing the diet with resveratrol can efficiently remove free radicals and improve the activities of Superoxide Dismutase (SOD), Catalase (CAT), and Glutathione

Peroxidase (GPX). Research proves that the main way in which resveratrol safeguards cells is by decreasing the amounts of Reactive Oxygen Species (ROS) in the mitochondria.[85,86]

In an animal model, a recent study revealed that resveratrol improved the liver's ability to counteract oxidative stress and reduce inflammation caused by persistent, unpredictable moderate stress-induced depression. These findings indicate that glutathione levels, Malondialdehyde (MDA) levels, NF-kB activity, TNF-α levels, and myeloperoxidase activity have returned to their normal states, confirming the truth of the matter. The use of resveratrol demonstrated a drop in iNOS mRNA and protein expression in LPS-stimulated intestinal cells that was dependent on the dosage. This led to a reduction in the generation of NO. Resveratrol significantly reduced the levels of iNOS and IL-6 in RAW264.7 cells that were stimulated with LPS, and this response was dependent on the dosage. As a result, it inhibited the generation of NO and the secretion of IL-6. Also, the presence of resveratrol resulted in a decrease in the generation of iNOS mRNA and protein in intestinal cells that were activated by LPS.[87] The decrease in the generation of Nitric Oxide (NO) was directly related to the dosage, demonstrating a dose-dependent reduction. Resveratrol displayed a decrease in the levels of iNOS and IL-6 in RAW264.7 cells that were stimulated by LPS, which was dependent on the dosage. Consequently, it inhibited the formation of Nitric Oxide (NO) and the secretion of interleukin-6 (IL-6).[88]

CONCLUSION

Several studies have been published on the principles of action and the possibility of flavonoids in inflammatory disorders, and active research is currently being carried out to examine these mechanisms. Flavonoids are a large collection of plant secondary metabolites that may be found in plant-based products including fruits, vegetables, and various components of plants. Flavonoids are also included in medicinal products. This article highlights the efficacy of several flavonoids in curing chronic inflammatory diseases. Flavonoids may mitigate chronic inflammation by inhibiting NF-κB activity and downregulating cytokines, chemokines, ROS, and enzymes at target sites. They achieve this by elevating antioxidant levels and lessening oxidative stress in the affected tissues. To summarize, flavonoids, which are dietary supplements with a range of health benefits, can be derived from a variety of natural sources, including foods. The gathering of papers may help researchers improve their present-day understanding of a variety of flavonoid molecules and the beneficial effect that these compounds have, even at the molecular level. This research focuses on studying the mechanisms of inflammation and its impact on illnesses that are mediated by inflammation.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ROS: Reactive Oxygen Species; **IFN-Y:** Interferon Gamma; **AP-1:** Activating Protein-1; **NF-β:** Nuclear Factor-Light Chain Enhancer of Activated B Cells; **SGLT1:** Sodium Dependent Glucose Cotransporter 1; **GLUT2:** Glusoce Transporter 2; **SLC16:** Solate Carrier Family 16; **SLC22A:** Organic Anion Transporters; **OATP1A2:** Organic Anion Transporting Polypeptide 1 A2; **OATP2B1:** Organic Anion Transporter 2B1; **OAT3 proteins:** Organic Anion Transporter 3; **LPH**: Lactase-Phlorizin Hydrolase; **CBG:** Capillary Blood Gas; **SULS:** Sulfotransferases; **COMTS:** Catechol-O-Methyltransferases; **HPLC:** High Performance Liquid Chromatography; **MS:** Mass Spectrometry; **NMR:** Nuclear Magnetic Resonance; **UHPLC:** Ultra High Pressure Liquid Chromatography; **NF-$_k$B:** Nuclear Factor Kappa Light Chain Enhancer of Activated B Cells; **IkB:** Inhibition of Nuclear Factor Kappa B; **GATA GATA:** Binding Protein; **cAMP:** Cyclic Adenosine Monophosphste; **IL-1β:** Interlukin-1-Beta; **IL-6:** Interlukin - 6; **TNF-α:** Tumor Necrosis Factor Alpha; **NO:** Nitric Oxide; **PLA2**: Phospholipase A2; **LOX:** Lipoxygenase; **COX:** Cyclooxygenase; **IL-17RA:** Interleukin 17 Receptor A; **FcεRI:** High Affinity IgE Receptor; **LPS:** Lipopolysaccharides; **ICAM:** Intercellular Adhesion Molecules; **VCAM:** Vascular Cell Adhesion Molecule 1; **HUVECS:** Human Umbilical Vein Endothelial Cells; **MAPKS:** Mitogen Activated Protein Kinases; **ERK:** Extracellular Signal Regulated Kinases; **JNK:** Jun N-Terminus Kinase; **Ikkβ:** Inhibitor of Nuclear Factor; **MMP-9:** Matrix Metalloproteinase-9; **IL-10:** Interleukin 10; **PGE2:** Prostaglandin E2; **MIP-1α:** Macrophage Inflammatory Protein-1 alpha; **MCP-1:** Monocyte Chemoattractant Protein-1; **PPAR-g:** Peroxisome Proliferator Actived Receptor Gamma; **STAT protein:** Signal Transducer Activator Of Transcription; **ELAM:** Endothelial Leukocyte Adhesion Molecule; **EC:** Epicatechin; **EGCG:** Epigallocatechin gallate; **MMP-3:** Matrix metalloprotein-3; **PKC:** Phospho-Protein Kinase C; **H2O2:** Hydrogen peroxide; **PRRS:** Pattern Recognition Receptor; **TLPS**: Toll-like Receptor; **PAMPS:** Pathogen Associated Molecular Patterns; **DAMPS:** Damage Associated Molecular Patterns; **SOD:** Superoxide Dismutase; **CAT:** Catalase; **GPX:** Glutathione Peroxidase; **MDA:** Malondialdehyde.

SUMMARY

The mechanisms of action and possible function of flavonoids in inflammatory illnesses have been studied extensively, with ongoing study. Flavonoids, found in fruits, vegetables, and plant parts, are a diverse group of secondary metabolites. Medicines include flavonoids. In this article, flavonoids are shown to alleviate chronic inflammatory disorders. Flavonoids may decrease chronic inflammation by blocking NF-κB and downregulating cytokines, chemokines, ROS, and enzymes at predetermined locations. Enhancing antioxidant levels and lowering oxidative stress in affected tissues has this effect. Flavonoids are natural supplements with several health advantages that may be found in foods. Researchers may learn more about flavonoid molecules and their molecular benefits from the studies. This research focuses on inflammatory processes and inflammation-related disorders.

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