REVIEW ARTICLE

The Role of Flavonoids in Mitigating Oxidative Stress: Mechanisms, Applications and Therapeutic Potential

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Abstract

Oxidation is a fundamental aspect of aerobic life processes, involving a reaction in which either electrons or hydrogen are transported from an element to an oxidizing mediator, resulting in the creation of free radicals. Oxidative stress is generally a result of an inequity between reactive oxygen species production and the antioxidant level of a biological system. This is the key factor in the advancement of numerous pathological conditions, such as cardiovascular and neurodegenerative disorders. Flavonoids are an extraordinary class of plant secondary metabolites that have been traditionally utilized as medicines, offering scientifically validated therapeutic benefits. The use of phytochemicals, particularly flavonoids, in the prevention and treatment of diseases is well recognized. Fruits, as well as green vegetables, are natural sources of flavonoids. For humans, recent studies have primarily concentrated on the beneficial effects of flavonoids on well-being. The flavonoids are classified into six different subclasses based on their ring structure. In the present review work, we have focused on the effect of flavonoids and its mechanism in reducing oxidative stress and, ultimately, various disorders. Flavonoids mainly produce their antioxidant effect through neutralizing free radicals, inhibiting enzymes responsible for the generation of free radicals, formation of chelates with metal ions, and stimulating the internal antioxidant defense system. We have also highlighted the therapeutic potential of flavonoids as future therapeutic agents.

Key words: Antioxidants, flavonoids, free radicals, oxidative stress, reactive oxygen species

INTRODUCTION

Over time, humans have encountered numerous diseases and challenges, leading to various efforts and strategies to combat them. One of the many approaches used to combat ailments is the utilization of medicinal plants to treat a varied form of diseases. Despite advancements in major therapies, the growing concerns over the rising toxicities associated with conventional treatments have led to an increasing shift toward herbal medicine. In recent times, medicinal plants have been regarded as complementary and alternative therapies used alongside other treatments.[1,2]

Unceasingly, the human body is exposed to oxidation reactions in which free radicals are in the form of reactive oxygen species (ROS) as well as reactive nitrogen species (RNS) that are generated internally during the usual metabolic activities of cells. Such reactive species can also arise from diseases or external factors such as smoking tobacco, pollutants of the environment, medicines, radioactive exposure, extreme alcohol consumption, and additional unidentified causes. Altogether they all play a crucial part in the cell signaling process and also protect against microorganisms, making them essential for maintaining homeostasis. When present in excessive amounts, the above-mentioned reactive substances can engage with and specifically damage the structure as well as the function of components of cells, which includes carbohydrates, lipids, further proteins, ribonucleic acid, and deoxyribonucleic acid as well.[3,4]

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Phytoconstituents are a potent group of chemicals classified as secondary metabolites in florae, encompassing a wide variety of chemical compounds such as flavonoids and polyphenols, as well as steroidal saponins. Numerous plant metabolites have been evaluated in the cells of animals and humans, revealing fascinating pharmacological activities. Phenolic compounds are known as utmost capable molecules for research in the field of human health promotion. These phytochemicals encompass a wide variety of molecules with more than 10,000 distinct structures and play significant parts in the lifespan of plants. The aforesaid compounds can be a collection of phenolics, lignans, tannins, stilbenes, lignins, and flavonoids.[5,6]

OXIDATIVE STRESS

Oxidative stress plays a crucial part in triggering diabetes, obesity, cardiovascular diseases, and a range of other chronic conditions. Oxidative stress can result from a disparity among the creation of free radicals, principally ROS, and the capacity of the body to counter these harmful molecules using antioxidants. The radicals such as superoxide (O^{2-}) and hydrogen peroxide (H_2O_2), as well as hydroxyl (•OH) and singlet oxygen, are generally recognized as ROS, which are produced as by-products of metabolic reactions in biological systems.[7] Some of the procedures, such as apoptosis, protein phosphorylation of proteins, immunity, activation of various transcription factors, and differentiation, rely on the proper creation and occurrence of ROS within cells, which must be maintained at minimum levels. The production of ROS primarily rests on enzymatic as well as non-enzymatic reactions. The enzymatic reactions that produce ROS include reactions involved in the respiratory chain, synthesis of prostaglandins, phagocytosis, and cytochrome P450 system as well. Cellular antioxidants such as glutathione, along with antioxidant enzymes such as superoxide dismutase and catalase, as well as glutathione peroxidase, capture both ROS and RNS to preserve an optimum equilibrium of the cell's redox state.[7,8] Maintaining this balance is essential for normal cellular function, as antioxidants neutralize reactive species generated during various metabolic processes. Although ROS serve as important signaling molecules at normal levels, their excessive production during oxidative stress can lead to considerable cellular damage and give rise to chronic disorders such as Alzheimer's disease, diabetes, obesity, Parkinson's disease, and neurological disorders.[9]

Oxidative stress also plays a part in the production of advanced glycation end products (AGEs), leading to harmful structural changes in proteins and nucleic acids. The AGEs are generated by non-enzymatic reactions between amino groups of proteins and the carbonyl groups of reducing sugars, followed by additional modifications of protein inclusive of glycoxidation reactions. As a result, oxidative stress offers a significant part in the creation of AGEs and the development of chronic disorders.[10,11]

FLAVONOIDS

They are a group of significant secondary metabolites that are commonly found in various cereals, most of the fruits and flowers, green vegetables, medicinal plants, nuts, and seeds. Flavonoids have demonstrated beneficial pharmacological and antioxidant effects on a variety of diseases, including inflammatory, cardiovascular, and neurodegenerative disorders, as well as cancer and diabetes. Flavonoids are linked to a wide range of health-enhancing effects, and they are an essential constituent in various cosmetology, pharmaceuticals, medicinal, and nutraceutical applications. These results are primarily due to anti-inflammatory, and antioxidant properties, along with their ability to regulate the vital cellular enzyme's functions. Flavonoids are produced through the metabolic phenylpropanoid pathway and consist of 15 carbon atoms arranged into three rings (C6–C3–C6), nominated as A, B, and C. [Figure 1 represents the basic structure of flavonoids]. Flavonoids serve protective functions against abiotic as well as biotic stresses. The primary includes cold, ultraviolet (UV) radiation, drought, salt, and heavy metals, and the latter includes herbivores as well as bacteria and fungi. Flavonoids are categorized in different forms based on their chemical structure, level of unsaturation, and the carbon ring oxidation state. Figure 1 represents the structure of flavonoids.[12,13]

The flavonoids are classified into six groups according to their basic ring structure, as depicted in Figure 2. They also possess beneficial effects on the health of humans and animals, with current interest focusing on their potential in disease treatment and chemoprevention. Some of the examples of flavonoids having antioxidant potential are presented in Table 1.

FLAVONOIDS AND ROS REDUCTION

Flavonoids exhibit numerous biochemical properties, with their most well-documented characteristic being their ability to function as antioxidants. The arrangement of functional groups around their core chemical structure influences the antioxidant properties of flavonoids. Antioxidants primarily function by delaying, preventing, or repairing oxidative

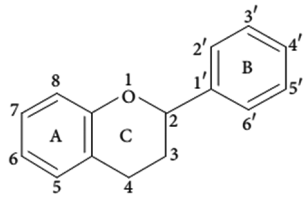

Figure 1: Basic structure of flavonoids.[12]

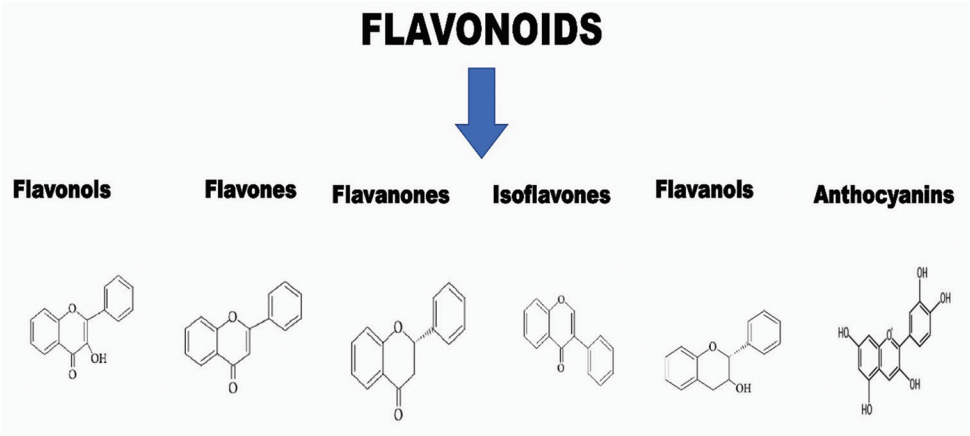

Figure 2: Classification of flavonoids.[7]

Table 1: Examples of flavonoids, their subclass and sources

S. No.	Subclass	Flavonoids	Source	References
1	Flavonol	Kaempferol Rutin, Morin, Quercetin, Myricetin	Fruits, such as apples, berries, cherries, and grapes, red wine, and olive oil	[12]
2	Flavones	Acacetin, Apigenin, Baicalein, Chrysin, Diosmetin Luteolin, Tricin, Wogonin	Fruits, such as navel oranges, oregano, and vegetables, such as carrots, green pepper, broccoli, olive oil, tea, peppermint, and rosemary	[13]
3	Flavanones	Eriodictyol, Hesperidin, Liquiritigenin, Naringenin, Naringin, Prunin, Silymarin	Fruits such as lemon and grapes. Medicinal plants	[14]
4	Isoflavones	Daidzin, Daidzein, Formononetin, Genistin, Glycitein, Genistein	Legumes, milk products, soybeans, tofu, and tempeh	[15]
5	Flavanols	Catechins, Epicatechin, Gallocatechin, Epigallocatechin	Apple, banana, black and green tea, chocolate, red wine, and lemon	[16]
6	Anthocyanins	Apigenidin, Cyanidin, Delphinidin, Pelargonidin, Petunidin, Malvidin, Peonidin	Berries, dry fruits and sweet potatoes.	[12,13]

damage to a target molecule.[17,18] The overall mechanism of action of flavonoids encompasses:

(i) Neutralizing free radical species (free radical scavenging)
(ii) Formation of chelates with metal ions
(iii) Inhibiting enzymes involved in free radical production and
(iv) Activating endogenous antioxidant enzymes.[17-19]

The most well-documented antioxidant effects of flavonoids stem from their capacity to unswervingly neutralize ROSs. Neutralization of free radicals by flavonoids occurs directly by contributing a hydrogen atom or through the transfer of a single electron. Another potential mechanism of action for flavonoids is their ability to chelate transition metal ions. Flavonoids possess chelating properties due to their binding capability to metal ions in the human body, thereby preventing these ions from participating in oxidation processes. Some flavonoids have the potential to chelate trace metal ions such as Fe^{2+} and Cu^{+}, which are crucial in oxygen metabolism and the generation of free radicals.[19]

Flavonoids can also function as intracellular antioxidants by inhibiting enzymes that generate free radicals, such as cyclooxygenase. lipoxygenase, protein kinase C, xanthine oxidase, and several others. Another possible mechanism by which flavonoids function as antioxidants is by inducing internal antioxidant enzymes. The metabolizing enzymes of Phase II reactions such as glutathione S-transferases, glucuronosyltransferases, sulfotransferases, N-acetyltransferases as well as methyltransferases serve as the primary defense against intracellular toxins and xenobiotics. Flavonoid activity encompasses many of the mechanisms listed above. Some of their effects may result from a combined property of neutralization of free radicals and interaction with the functions of enzymes.[20,21]

THERAPEUTIC APPLICATION AND POTENTIAL OF FLAVONOIDS

Plants generate a wide range of organic compounds; most of them are not involved directly in the growth and development

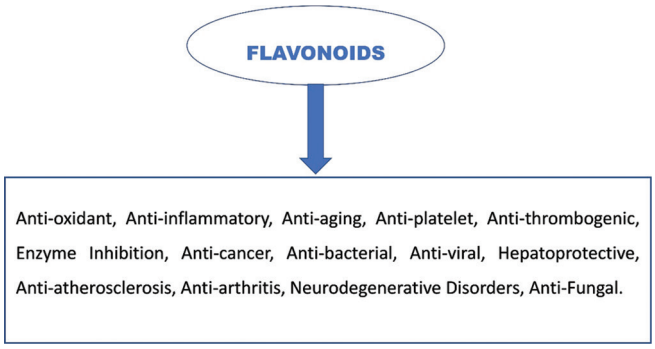

Figure 3: Distinct therapeutic potential of flavonoids

of plants. These organic compounds, commonly known as secondary metabolites (such as flavonoids), are often found in specific taxonomical sets within the plant kingdom. Numerous flavonoids have been established as bioactive constituents that chiefly affect nucleic acids or proteins, exhibiting antimicrobial, insecticidal, and varied pharmacological properties. As a result, flavonoids are of interest in both medicines, where they are explored as therapeutics, and in agriculture, where they are considered for use as pesticides. Flavonoids are believed to have health benefits as a dietary component, thanks to their strong antioxidant properties in both *in vitro* as well as *in vivo* systems. Flavonoids can stimulate protective enzyme systems in humans. Several studies have indicated that flavonoids may offer protective effects against various infectious diseases (both bacterial and viral) as well as degenerative conditions, including cardiovascular diseases, cancers, and other age-related ailments. Flavonoids are commonly used in cosmetics mainly for their antioxidant and soothing benefits. Their cosmetic applications focus on three main areas: Protection from sunlight (UV rays), anti-aging effects, and anti-inflammatory properties.[12,15]

Studies in both animals and humans have consistently shown the anti-inflammatory as well as antioxidant properties of polyphenols which provide a strong basis for utilizing them in the prevention and treatment of several non-communicable diseases. These diseases cover an extensive range of conditions such as cancers, inflammatory and cardiac disorders, metabolic and gastrointestinal disorders, as well as neurodegenerative and autoimmune diseases. Many studies have shown that dietary polyphenols are essential in blocking proinflammatory transcription factors by interacting with proteins involved in the expression of genes or cell signaling. This interaction helps prevent various chronic diseases linked to inflammation. Recent research suggests that long-term consumption of polyphenols can help protect against the development and progression of these health conditions. Polyphenols have notably emerged as promising agents for reducing oxidative stress, with *in vitro* studies highlighting their effectiveness in combating oxidative damage.[18,22,23]

Over the past decade, flavonoids have garnered significant attention in the literature, with a range of potential beneficial effects being identified. The protective effect of phytochemicals, specifically flavonoids against chronic diseases, may be attributed to their antioxidant properties, which help counteract the damaging effects of excess oxidants such as ROS and RNS. In current years, many epidemiological and case–control studies have explored the mechanistic interactions, highlighting the diverse benefits of flavonoids.[12,23] In Figure 3, the proven therapeutic potential of flavonoids by previous researchers is presented.

CONCLUSION

Flavonoids are specifically a cluster of constituents naturally present in many plants, including fruits, vegetables, and plant-based products such as coffee and chocolate. It has been consistently reported that flavonoids offer a broad range of health benefits. A diverse class of flavonoids originate in nature each having their unique physical and chemical as well as biological properties. The relationship based on the structure and function of flavonoids exemplifies their significant biological activities.[23,24]

Therefore, incorporating different types of flavonoids into your daily diet is strongly recommended to maintain health and reduce the risk of several life-threatening diseases. More intense approaches should be used to enhance the bioavailability of flavonoids. Future advancements will offer fresh insights and undoubtedly pave the way for a novel age of pharmaceutical agents based on flavonoids for treating various infectious and degenerative diseases.

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