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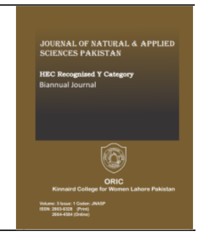

BIOFLAVONOIDS; THEIR SOURCES AND NUTRACEUTICAL MANEUVERS

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Abstract

Bioflavonoids, the phenolic compounds, have gained tremendous attention in the field of research because of their enormous applications especially in the field of food sciences. Chief dietary sources of bioflavonoids are fruits and vegetables that provide a variety of health benefits to the consumer as well as act as growth promoters and help in combating oxidative stress. In the reaction to the low production potency from the plants, scientists have directed their concentration towards the assembly of flavonoids in microorganisms by employing metabolic engineering and artificial biology, hence producing more bioflavonoids for further applications. Moreover, along with the ability of their organoleptic properties, they are being used as medicine such as in the prevention of cancer, gastrointestinal ailments, diabetes, and have notable radical scavenging, anti-ulcerogenic, hepatoprotective, anti-inflammatory, and antimicrobial activity. Bioflavonoids are provided with a helpful role against cardiovascular diseases by working as vaso-relaxant, antiatherosclerotic, anti-thrombogenic, cardio-protective, and antineoplastic agents. The present review summarizes the data of the past decades based on potential source and nutraceutical health benefits of bioflavonoids with the latest studies.

1. Introduction

Bioflavonoids are the phenolic compounds belonging to a major class of secondary metabolites, with a vast array of structures and they are accountable for the chief organoleptic properties of food and beverage derived from plants. Flavonoids are based over one of the most important groups of plant phenolic which were considered the point of attention 50 years ago when the work on the flavonoid mechanism was started and now more than 8000 flavonoids are present (Mulvihill & Huff, 2016). The concept is known for centuries that the compounds that originated from plants have a vast array of biological significance. A scientist Szent-Gyorgyi in 1930 discovered a novel substance from the family of oranges and named it vitamin P. Later it has appeared that the substance was actually a flavonoid (Lee *et al*., 2005). The letter "P" was given to this group for the permeability factor, as they enhance the integrity and permeability of capillary lining.

Bioflavonoids, mainly yellow-colored, aromatic plant pigments, originate from the Latin word "flavus" which means yellow. These water-soluble substances on the molecular weight range of 300 to 700, having basic skeleton comprises 15 carbon atoms and are generally called "vitamin-like" substances, whose basic structure is shown in Figure 1 (G.Bruno *et al*., 2002) (Mulvihill & Huff, 2016). Flavonoids gain more interest at the time of the French Paradox where in the Mediterranean population an obvious decrease was observed in the cardiovascular disease prevalence allied with the consumption of red wine and saturated fats.

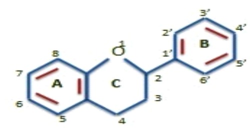

Figure 1: Basic structure of bioflavonoid

2. Bioflavonoids Natural Sources

Strawberries and red grapes are naturally packed with an abundant amount of bioflavonoids, providing beneficial functioning concerning described health benefits (Giampieri *et al*., 2015; Kim *et al*., 2015; Park *et al*., 2015). Recent research studies reported that apple polyphenols aid in the prevention of spikes in blood sugar through various mechanisms. Flavonoids present in apples majorly include quercetin and traces of other flavonoids as well, which inhibit alpha-glucosidase and alpha-amylase, as these enzymes are responsible for the breakdown of the complex carbohydrates into simple sugars. So ultimately this can reduce the absorption of sugar into the body which is a good sign for diabetic patients (Awad *et al.,* 2000). Peaches contain an abundant amount of bioflavonoids polyphenolic antioxidants including ß-cryptoxanthin, lutein, and zeaxanthin. These compounds work as defensive scavengers against reactive oxygen species (ROS) and oxygen-derived free radicals, playing an important role in various disease processes (Upadhya *et al.*, 2015).

The tomato family is provided with plenty of useful components for a healthy life, bioflavonoids are one of their chief components (Muniz *et al*., 2015). Moreover, in several studies, it is illustrated that quercetin is found to be the chief flavonoids found in garlic, onions, and leeks, and is utilized in our daily routine. As quercetin is known for its sparking potential to boost up the immune system as well as it has been taking place in top scores of potent antioxidants (Ayaz & Alpsoy, 2006). All affiliates of the tea family are sufficiently enriched as well as naturally provided with a special assemblage of bioflavonoids including catechin, epigallocatechin, epicatechin, and epicatechin gallate. In diabetes prevention, they play their imperative role, as well as direct work on replicating DNA sequences to prevent mutations, which can lead to cancer (Chakraborty *et al.*, 2015). Bioflavonoids in our daily diet are also found in cereals and herbs, presenting no side effects, but just benefit (Yakubu *et al*., 2015).

2.1 Flavonoids Production from Microbes

In the reaction to the low production potency from chemical and plants synthesis, scientists have directed their concentration to the assembly of flavonoids in microorganisms by employing metabolic engineering and artificial biology (Y. Wang *et al.*, 2011). The chemical synthesis of flavonoids needs intense reaction conditions and virulent chemicals (Park *et al*., 2009). Attributing to the rapid development in biological science and also the flooding of genome info from a range of organisms, combinatorial biosynthesis proposes a bonus for the production of uncommon and pricy natural products(A. Wang *et al*., 2010). Many of the prokaryotes and eukaryotes including *Saccharomyces cerevisiae*, *Phellinusigniarius*, *E. coli*, *Streptomyces venezuelae*, and medicinal mushrooms, are used for flavonoids production (Du. Zhang, *et al*. 2011).

2.2 Phenylpropanoid Pathway

Naringenin chalcone, in plants, is the precursor for an outsized range of flavonoids made from phenylpropanoid (PP) artificial pathways. Production from fermentation through E.coli, carrying artificially arranged phenylpropanoid pathway, is the primary example to point out an almost complete synthesis of plant biosynthetic pathway in the heterologous microorganism for bioflavonoid production from the amino acid precursors, tyrosine and phenylalanine (Hwang *et al*., 2003). As the primary step in the plant PP pathway, cinnamic acid is produced by the activity of phenylalanine ammonia-lyase (PAL) after the deamination of phenylalanine. Cinnamate-4 hydroxylase (C4H) hydroxylates the cinnamic acid to *p*-coumaric acid and through the action of 4-coumarate: CoA ligase it is activated ultimately to the *p*-coumaroyl-CoA. Chalcone synthase (CHS) after catalyzing the malonyl-CoA acetate units along with *p*-coumaroyl-CoA produces naringenin chalcone which is then converted to naringenin (Austin & Noel, 2003).

3. Bioflavonoids and Their Nutraceutical Health Benefits

3.1 Flavonoids and Their Medicinal Chattels

Bioflavonoids account for the chief active medicinal ingredient found in plants. Like other phenolic compounds, they typically show a persuasive antioxidant action. They also show antiallergenic, antiviral, anti-inflammatory, hepatoprotective, anticarcinogenic, and antithrombotic activities as well as have long been renowned as potent metal chelators, as reviewed in the following subsections:

3.2 Antioxidant Property of Bioflavonoids

A well-known character of nearly every group of bioflavonoids is their ability to perform as an antioxidant among which catechins and flavones are considered to be at the top of the list against reactive oxygen species (ROS) hence protecting the body. The ROS and free radicals which are persuaded by any exogenous damage or by usual oxygen metabolism, incessantly intimate the body tissues and cells by damage (Groot, 1994; Grace, 1994) (Pandey *et al*.,2016). ROS and free radicals incremented large numeral human diseases (*Wegener* & *Fintelmann, 1999; Ares*and *Outt*, 1998; Lee *et al*., 2005). Some bioflavonoids such as rutin, morin, quercetin, myricetin, and kaempferol act as potent antioxidants, providing anticancer, anti-allergic, anti-inflammatory, and antiviral properties. Moreover, they are also known to play a significant role in the treatment of cataracts, cardiovascular and liver diseases. Silytin and Quercetin have been suggested to exert a protective effect by performing a free radical scavenger role in liver reperfusion ischemic tissue damage (Pandey *et al.,* 2016). The scavenging activity of some flavonoids is led by myricetin on top, having the highest scavenging activity, followed by quercetin having slightly lower scavenging activity than myricetin, subsequently followed by rhamnetin, morin, diosmeti, haringenin, apigenin, catelhi, 5, 7-dihydroxy-3, 4, 5-trimethoxyflavones ribinin, kaempferol and flavone have least scavenging activity respectively (Ratty & Das, 1988).

4. Antimicrobial Potential of Bioflavonoids

The antifungal, antibacterial, and antiviral properties of biophenols and phenolic acid esters were reviewed. Flavonoids extracted from orange peel were found to be fungicidally active against Deuterophoma tracheiphila, as shown by particular tests. Hesperidin showed a slightly stimulated fungal growth, whereas langeritin showed weak activity and nobiletin showed strong activity. Chlorflavonin is a flavonoid type antifungal, first to contain chlorine having antibiotic action, is produced through the Aspergillus candidus strains (Pandey *et al*., 2016; Ten Cate *et al.,*1973)**.** Plant phenolics have great potential against a wide array of microorganisms (Khan *et al*., 2015). The antiviral activity of bioflavonoids has been originated since the 1940s, but now efforts are made to create synthetic compounds by modifying natural ones to their antiviral activity. Hesperidin, quercetin, catechin, dihydroquercetin, morin, apigenin, and rutin are recognized as antiviral against 11 types of viruses (Selway, 1986) Antiviral activity depends upon non-glycosidic compounds. It is documented that flavonols are more effective against the herpes simplex virus (type 1) as compared to flavones, in which galanin have most important and is followed by kaempferol while the least important one is quercetin (Thomas *et al*., 1998). A natural Bioflavonoid polymer, having a molecular weight of 2100 dalton, has been considered actively against Type 1 and Type 2. Herpes simplex viruses straines (Babii *et al*., 2016; Loewenstein, 1979). Another investigation has been made for the application of bioflavonoids against a super prevailing HIV (Huang *et al*., 1997). Bioflavonoids were also found to have anti-AIDS activity. It has been tested that out of 28 flavonoids the flavans were considered to be more effective in discriminatory inhibition of HIV-1 and HIV-2 than flavanones and flavones (Castro-Vazquez *et al*., 2016).

5. Effect on the Gastrointestinal System

5.1 Antiulcerogenic Potential

Recent studies have designated flavonoids to have antiulcerogenic potential. Flavonoid glycosides of Labiatae potentially reduce ulcer index with the inhibition of pepsin and gastric acid in aspirin-persuaded ulcers among rats (Alarcon *et al.*, 1994). Kaempferol, quercetin, and rutinintraperitonial administration (25-100 mg/kg) significantly prevented the dose-dependent gastric injury in rats caused by acidified ethanol (Castro-Vazquez *et al*., 2016; Izzo *et al*., 1994).

Acute or lethal damage to the liver through various substances such as galactosamine, phalloidin, ethanol, CCl_4, and other compounds, and this injury can be controlled by the bioflavonoids having a potential hepatoprotective response. According to a study that investigated the reputed remedial action of apigenin, naringenin, silymarin, and quercetin against hepatotoxicity induced by microcystin LR, the most effective one was found to be silymarin (Carlo *et al*., 1993). In investigational cirrhosis, the bioflavonoid, veneration, and rutin have shown hepatoprotective and regenerative effects (Castro-Vazquez *et al*., 2016; Lorenz, *et al*., 1994).

5.2 Anti-Inflammatory Potential

The anti-inflammatory potential of flavone/flavonol glycosides and flavonoid aglycons have been reported to impart anti-inflammatory action in case animals of both chronic and acute inflammation when applied topically or given orally (Lee *et al*., 1993; Michel *et al.*, 2016). A citrus flavonoid known as hesperidin imparts analgesic and anti-inflammatory effects significantly (Shahid *et al.*, 1998). Moreover, according to recent research quercetin, apigenin and luteolin are reported to have a potent anti-inflammatory role (Formica &

Regelson, 1995). It is documented by researchers that arachidonic acid metabolism can be modulated by the inhibition of lipooxygenase activity (LO) and cyclo-oxygenase (COX). It is also hypothesized that the inhibitory action of flavonoids on the metabolism of arachidonic acid results in their anti-allergic and anti-inflammatory properties (Ferrandiz & Alcaraz, 1991). It is reported that among all the flavones myricetin, kaempferol, fisetin, and quercetin possess lipoxygenase activity and cyclo-oxygenase inhibitory action (Kim *et al*., 1998; Jachak, 2001).

5.3 Antidiabetic Effects

Bioflavonoids acquire antidiabetic action, especially quercetin. It follows the mechanism of pancreatic islets regeneration and increases the release of insulin studied in diabetic rats by streptozotocin induction (Vessal *et al.*, 2003). In another study, it is reported that quercetin enhances the uptake of calcium as well as motivates the release of insulin especially in the case of non-insulin-dependent diabetes (Hii & Howell, 1985; Michel *et al*., 2016).

6. Applications of Bioflavonoids For The Cardiovascular System (CVS)

6.1 Vaso-Relaxant Effect

Flavonoid consumption leads to the enhancement of the vaso-relaxation process, preventing endothelial dysfunction, which ultimately leads to a decrease in arterial pressure. (Iijima & Aviram, 2001; Bernatova *et al*., 2002). The endothelial dysfunction plays a potent role in the commencement of cardiovascular disease (CVD) with the development of arterial thrombus and atherosclerosis as major complications (Jayakody *et al.*,1985). Another study reported that the consumption of bioflavonoids prevents CVD with atherosclerosis as well as hypertension. Many other documentations support the fact that the phenolic compounds have the potential to induce a vasorelaxant effect in rats and decrease arterial pressure. Bioflavonoids, especially *Anthocyanin delphinidin*, persuade endothelium-dependent vasorelaxation effect in subjected organisms (Andriambeloson *et al*., 1997; Grassi *et al.*, 2016).

6.2 Antiatherosclerotic Agent

In the initiation of atherosclerosis, the oxidation of low-density lipoprotein (LDL) induced by the reaction of free radicals results in their modification and this serves as an initial step in the commencement of the disease. This oxidation-induced-modified LDL is rapidly uprooted through the scavenger receptors which lead to foam cell formation. Here, the bioflavonoids act as a chain-breaking antioxidant and scavenge some of the radical species directly (Basu, Das, *et al*., 2016). Among all the bioflavonoids, quercetin and its glycosides play a potent role in the prevention or protection of oxidative modification of LDL. (Fuhrman *et al.*, 1995). Moreover, a Japanese study supported the opposite relation of total plasma cholesterol (TPC) concentration and bioflavonoid intake (Arai *et al*., 2000).

6.3 Antithrombogenic Agent

Platelet aggregation plays a polar role in the case of thrombotic diseases. Oxygen-free radicals and lipid peroxides were generated by the activated platelets which adhere to the vascular epithelium. These peroxides and free radicals restrain the endothelial formation of nitrous oxide and prostacyclin. It was reported in the 1960s that the pigments of tea can enhance fibrinolysis, decrease blood coagulability and prevent platelet aggregation and adhesion (Lou *et al*., 1989)**.** In another study, some selected bioflavonoids such as kaempferol, myricetin, and quercetin significantly inhibit platelet aggregation in monkeys and dogs (Osman *et al.,* 1998)**.** Bioflavonoids properly maintain the concentration of nitric oxide and prostacyclin by directly scavenging free radicals, thus show an antithrombotic effect (Gryglewski *et al*., 1987)**.** Moreover, they inhibit the activity of lipoxygenase and cyclooxygenase pathway, thus acting as in vivo and in vitro antithrombotic agents (Alcaraz & Ferrandiz, 1987; Warner *et al*., 2016)**.**

6.4 Cardio-Protective Impact

Recent concentration in flavonoids has been stirred up by the potential health advantages arising from the antioxidant action of polyphenolic compounds. These are the results of their high tendency of transferring chelate metal ions, electrons, and scavenge reactive O_2 species (Almeida *et al*., 2016; Kandaswami & Middleton Jr, 1994)**.** Owing to these properties, bioflavonoids are thought to be the potential protectors of the heart against chronic cardiotoxicity rooted in the cytostatic drug doxorubicin. This doxorubicin could be an efficient antineoplastic agent; however, its clinical use is prescribed by the incidence of accumulative dose-related cardiotoxicity, leading to congestive heart failure. A recent study documented that the cardio-toxicity of doxorubicin on the left atrium of a mouse has been subdued by the bioflavonoids, 7- monohydroxyethylrutoside and 7’,3’,4’- trihydroxyethylrutoside (Almeida Rezende *et al*., 2016; Lackeman *et al.,* 1986).

6.5 Antineoplastic Impact

A decent variety of bioflavonoids have shown antineoplastic activity. Numerous recent reviews have illuminated this activity. Elaborated studies have discovered that quercetin applies a dose-reliant inhibition of growth as well as colony formation (Kontruck *et al*., 1986). Some bioflavonoids such as kaempferol, taxifolin, catechin, and fisetin additionally suppressed the cell growth (Kim & Shin, 2015). On screening the antileukemic efficaciousness of twenty-eight naturally present and artificial flavonoids on human promyelocytic leukemic HL-60 cells, genistein, the isoflavone was found to possess sturdy effect (Hirano *et al*.,1994; Swanson, 2016).

7. Conclusion

Cure and prevention of illness through phytochemicals particularly bioflavonoids is well known. Naturally, they are present in various fruits and vegetables including apples, peach, strawberry even among cereals as well imparting color and flavor along with nutritional characters (Petersen *et al*., 2016). Bioflavonoids account for the chief active medicinal ingredient found in plants. Like other phenolic compounds, they typically show a persuasive antioxidant action. They also show antiallergenic, antiviral, anti-inflammatory, hepatoprotective, anticarcinogenic, and antithrombotic activities as well as have long been renowned as potent metal chelators. Diversity of bioflavonoids instituted in nature acquires their chemical, physical and physiological properties. The medicinal efficiency of various bioflavonoids as anti-ulcerogenic, anti-cancer, antidiabetic, cardiovascular diseases prevention, and antimicrobial agents is well recognized. In developing countries, they are used commonly, while their therapeutic potential and the use of newly derived compounds must be validated by employing some specific biochemical tests (Zheng *et al.*, 2016). On the other hand, it is easier to produce a large number of bioflavonoids through microbial means. Supplementary research is needed to provide innovative insights which will surely escort us to a novel era of bioflavonoid-based pharmaceuticals for the cure and management of various degenerative and infectious ailments.

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