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THE ROLE OF FLAVONOIDS IN DRUG DISCOVERY- REVIEW ON POTENTIAL APPLICATIONS

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ABSTRACT: Natural products have been playing an important role in our health. Among these, flavonoids comprise one of the most appearing botanical products. Different three dimensional shape, chemical, physical and biochemical properties of flavonoids can interact with different sub cellular locations to influence biological activity in plants, animals, and microbes. A series of flavonoids had showed inhibitory activity against a variety of human pathogens, and they used as curing agents for various human diseases. This review has presented some pharmacological activities of flavonoids and collectively referred as new potential drug leads.

KEYWORDS: Flavonoids, Antioxidants, Antiulcer, Antiviral, Antibacterial, Anticancer.

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1. INTRODUCTION

Flavonoids are chemical entities present in plant kingdom and are secondary metabolites with variable poly phenolic structures. These phenolic compounds are commonly found in fruits, vegetables, grains, barks, roots, stems, flowers [1, 2]. They exhibit wide range of structures and play role on the characteristics of plant derived foods and beverages. Over 5000 naturally occurring flavonoids have been characterized from various plants. They are classified into six subgroups: Flavones, Flavonols, Flavanones, Isoflavones, Chalcones and Anthocyanins. They are associated with the plant physiology. Plant hormones are transported by the influence of flavonoids. They are involved photosensitization, photosynthesis and physiological survival of plants [3]. Usually different

chromatographic techniques, UV, IR, Mass, NMR detectors are generally used for the separation, quantification, and identification of flavonoids [4]. Flavonoids drew compulsion on their research after French paradox which is phrase or expression related to the observation of low coronary heart disease (CHD) death rates despite high intake of dietary cholesterol and saturated fat [5]. The flavonoids in red wine are responsible, at least in part, for this effect [6]. Flavonoid molecules of varying structures are capable of altering the biological activity of enzymes and cell systems in human beings and they are revealed as antioxidant, antiviral, anti-inflammatory, antibacterial, antiallergic activities.

Flavonoids as Antioxidants

Flavonoids are well known and widely used antioxidants from plants. Flavonoids protect cells from oxidative effect caused by reactive oxygen species (ROS) [7, 8].The imbalance between oxidants and antioxidants contribute to the oxidative stress on the organism and are involved in many pathological processes such as inflammation, atherosclerosis, cancer, aging, etc [9,10].The free radical scavenging and antioxidant activity of plant flavonoids has been reviewed [11, 12, 13].In 2002 Heim et al., observed that in Catechol (o-dihydroxy) group in ring B, aroxyl radicals are highly stable through H-bonding and participate in electron dislocation. 3', 4'-catechol structure in B-ring strongly enhances lipid peroxide inhibition and this arrangement is an important characteristic of most potent scavengers of peroxyl, superoxide and peroxy nitrite radicals and its absence decreases antioxidant activity [14].Thus the hydrophilic/lipophilic balance is of some importance for antioxidant properties of flavonoids. The absence of the hydroxyl group at position 3 in flavanones and flavones decreases their antioxidant ability. Hydrogen donating ability is assigned to this activity. In fact, the phenolic groups of flavonoids are the source of a readily available 'H' atoms such that the subsequent radicals produced can be delocalized over the flavonoid structure[15].Tapas et al. had observed that catechins and flavones appear to be the most powerful flavonoids for protecting the body against ROS [16].In1988 Ratty et al., found that the order of scavenging activity of flavonoids were myrcetin > quercetin > apigenin > catechin > robinin > kaempferol > flavones[17].Vegetables, fruits, and whole grains help to increase levels of antioxidants in the body[18].

Antiulcer activity of Flavonoids

Peptic ulcer occurs mainly in the stomach and the proximal duodenum. Ulcers were thought to be produced by stress hormones and they increases the glandular secretion which alter the nature of proteins in the walls of the blood vessels and it gets sufficiently weakened, then minute mechanical damage easily cause ruptures, resulting in leakage of blood into the tissue [19].The efficacy of several plants for the treatment of peptic ulcers were confirmed through clinical research and credited mainly to the presence of flavonoids. In 1970's antiulcer properties of chalcones were studied. Crude drug from the root of *Sophora subprostrata* protects the gastric mucosa from lesions. It was found that 2',4'-dihydroxy-3'-(3-methyl-2-butenyl)-4-(3-methyl-2-butenyloxy) chalcone, 2'-hydroxy- 4,4'-

bis(3-methyl-2-butenyloxy) chalcone and 2'-carboxymethoxy-4,4'-bis(3-methyl-2-butenyloxy) chalcone (sofalcone), showed strong activity[20,21]. Garcinol showed potent free radical scavenging activity and prevented acute ulceration in rats induced by indomethacin and water immersion stress caused by radical formation. In spite of the fact that the mechanism of its anti-ulcer activity of garcinol is not yet understood, it could scavenge reactive oxygen species on the surface of gastric mucosa [22,23].Quercetin (3, 3', 4', 5, 7-pentahydroxyflavone) protects the gastrointestinal mucosa from acute lesions induced by various factors. It increases the mucus production, growing PAF. Antihistaminic properties which helps to decrease histamine levels and reduction of the number of ethanol-induced mast cells by inhibition of lipid peroxidation and enhancement in the levels of mucosal non-protein SH compounds (important antioxidant agents). The main mechanisms of action for the gastro protective effects of this flavonoid were confirmed to be its antioxidant properties in a number of studies [24, 25, 26].

Flavonoids as Antivirals

Antiviral activity of flavonoids has been recognized since 1940s. Apigenin, Catechin, Dihydroquercetin (taxifolin), Hesperidine, Morin, Quercetin and Rutin had been reported to hold antiviral activity [27].Flavonoids possess antiviral effects since they can interfere with the different stages in the replication cycle of viruses [28].Some of the flavonoids affect the intracellular replication, and some of them inhibit the infectious properties. Most of the studies were performed in vitro and a few of flavonoids were found to be effective in vivo as well. In vitro studies done by Bae et al on *Macaccus Rhesus* Monkey Kidney cells MA104., revealed that flavonoids in their glycone forms were inhibitors on rotavirus infectivity but not in their aglycone forms [29].Natural flavonoids 3-O-methylgalangin, 7-O-methyleriodictyol and Pinocembrine were active against *Infetious Salmon Anemia Virus* propagated in monolayers of salmon head kidney cells (*SHK-1*) found that were active against *ISAV* on the in vitro evaluation. 3rd position of flavones skeleton occupied by methoxyl group was found to be essential for antirhinovirus activity [30]. In a study of medicinal plants against herpes simplex viruses by Khan et al revealed that 5,7-dimethoxyflavanone-4'-O-[2"-O-(5"'-O-trans-cinnamoyl)-β-D-apiofuranosyl]-β-D-glucopyranoside was very active against *HSV-1* . They were observed that the main structural discrepancy from other flavonoids was the B-ring of this compound has a cinnamoyl moiety [31].In 2012 a study was carried out in Malaysia, Quercetin and Baicalein were examined for their against Japanese encephalitis virus. *Vero* cell line resulting from African green monkey was used in this study. This study demonstrates that Baicalein has significant antiviral activities against the different stages of *in vitro* JEV replication [32].In the recent years antiviral activity of flavonoids focused on dengue virus type-2(DENV-2). C6/36 mosquito cell line derivative from *Aedes albopictus* and *Vero* (African green monkey kidney) cell line were used in this study. Bioflavonoids, quercetin, naringin, hesperetin and daidzein were analysed against dengue virus replication. Quercetin was reported to be the most significant antiviral active agent against

DENV-2 among the tested bioflavonoids. It was found to be antidengue activity of quercetin is due to its activity against the different stages of intracellular replication of DENV-2[33].

Flavonoids as Antibacterial compounds

Perhaps most widely studied and known biological effects of flavonoids are their antibacterial effects. Large numbers of flavonoids have antibacterial effects. In 2001 Narayana et al., observed that flavanones having sugar moiety does not show antimicrobial activity [34]. Examination of coumarins, flavonoids for antibacterial activity showed that baicalein, narigin and rutin had good antibacterial activity [35]. Flavonoids obtained from *Bolusanthus speciosus* had been effective against *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus*, *Candida mycoderma* [36].A study of Antimicrobial and anti-inflammatory activities of extracts and constituents of *Oroxylum indicum* by Ali et al., observed that Gram-negative bacilli Escherichia coli and Pseudomonas aeruginosa were inhibited by Chrysin (5,7-dihydroxyflavone), at a rate comparable to that of streptomycin[37,38].Gram-negative bacilli *Enterobacter*, *Klebsiella pneumonia* (*K pneumoniae*), *Proteus mirabilis* (*P mirabilis*), *Proteus vulgaris* (*P vulgaris*), *Ps aeruginosa*, *E coli* were inhibited by apigenin, vitexin, saponarin,apigenin, and lucenin 2-O-glycoside, and luteolin 7-O-glycoside[39].It had been observed that the growth of E coli could be inhibited by certain acetylated derivatives of quercetin, quercetin 3-arabinopyranoside-2”-gallate. Naringenin, the flavanone pinocembrin, isomeric compounds 5,7,4’-trihydroxy-6-methyl-8-isoprenylflavonone and 5,7,4’-trihydroxy 8-methyl-6-isoprenylflavonone and 3-O-methylquercetin showed activity against *S. aureus* in several studies[40,41,42,43]. Wang et al., examined the activity of a number of lipophilic flavonoids against *B. cereus* and were found that the presence of hydroxyl groups at positions C-5 and C-7 was very important for activity. It has been confirmed that Lipophilic flavonoids with hydroxyl groups at positions C-5 and C-7 was very important for activity, whereas the presence of an additional methoxyl group at C-7 or dihydroxyl groups at C-3’ and C-4’ significantly reduced activity[44].Isoflavonones containing prenyl groups had the highest activity against Gram-positive bacteria such as *S. aureus* and *B.subtilis*. Bojase et al., found that this activity was greatest when the prenyl groups were located at positions C-6 or C-8 in ring A and C-3’ or C-5’ in ring B [45].

Flavonoids as Anticancer compounds

Flavonoids are powerful bioactive molecules and they are obstructive leads for cancer treatment due to their ability to induce apoptosis [46]. CYP_3A_4, which is the most plentiful enzyme in the liver and beneficial in metabolizing a significant number of carcinogens and medications. Several studies revealed that Kaempferol, Quercetin , Apigenin, Naringin Quercetin and naringin can inhibit CYP_3A[47]. In recent years Intracellular signal transduction regulated cell growth and proliferation. The reaction is catalyzed by protein kinases. A possible mechanism for the potential anti-carcinogenic effects of flavonoids could be their ability to inhibit various PKs, thereby inhibiting signal transduction event of cell proliferation. Flavonoids genistein inhibit the epidermal growth factor

(EGF) and butein (20, 3, 4, 40-tetrahydroxychalcone) inhibit tyrosine kinases. In 2013, a study related to recent trends of flavonoids as anti-cancer potentials showed that PKC efficiently inhibited by flavones and flavonols having a 3', 4'-dihydroxy substitution on the B ring. Formation of reactive oxygen species (ROS) is a major step in the tumor promotion and progression stages. ROS play important role in DNA damaging and mutagenic signaling and act as secondary messenger in several pathways that lead to increase in cell proliferation, resistance to apoptosis. Flavonoids may exert part of their antioxidant and anti-inflammatory activities via direct inhibition of these prooxidant enzymes. Direct scavenging by flavonoid antioxidants of ROS inside or outside the catalytic pocket (with simultaneous oxidation of the flavonoids), chelation of the enzyme metal centers by the flavonoids, and enzyme inactivation by reactive aryloxyl radicals, quinones, or quinonoid compounds produced upon flavonoid oxidation that may eventually form covalent adducts with the enzyme[48].

CONCLUSION

Flavonoids are biologically active key components that were found abundantly in plant kingdom. Flavonoids constitute a number of dietary supplements as well as medicines. They are beneficial for general health. Improvements in isolation and structure elucidation of flavonoids have a great deal to bring many new compounds that have undergone clinical evaluation over the last few years. Natural and synthetic flavonoids alone or in combination will be fruitful against the most common diseases. Their general occurrence, broad spectrum multiplicity and natural origin make them suitable chemical scaffolds for novel drugs. This enhanced interest can be permanent only if natural products research can continue to be competitive with other drug discovery techniques.

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