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FLAVONOIDS: AN EMERGING POTENTIAL TARGET

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ABSTRACT

Flavonoids are the pigments that are widely distributed in plants fulfilling many functions. In recent years, Bioflavonoids have shown a number of important pharmacological activities such as anticancer, anticonvulsant, antibacterial, and antimicrobial and in various vascular diseases. They have remarkable antioxidant activity, which makes them a good contender for herbal therapy in different diseases. In view of their wide pharmacological and biological actions, they seem to have great therapeutical potential. Hence, the present review has been aimed to study the various therapeutic activities of bioflavonoid.

INTRODUCTION

Flavonoids are the naturally occurring polyphenolic compounds [1] which are responsible for imparting colour to the plants [2] The word flavonoid comes from the Latin word flavus, which means yellow [3]. They may vary in color like red, purple and orange. Flavanoids were discovered along with vitamin C, in 1928 by Albert Szent-Gyorgyi, who named them as vitamin p [4]. In United States the average daily intake of Flavonoids is between 150 and 200 mcg. Flavonoids have been reported to possess antioxidant properties and act as a free radical scavenger. Numerous medicinal plants contain varying amounts of flavonoids, which are used to treat various disorders of the peripheral circulation, to lower blood pressure, to improve aquaresis [5]. Further, bioflavonoid also possess anti-inflammatory, antispasmodic, and anti-allergic, antimicrobial activity. Hence, the present review has been designed to discuss various therapeutic effect of bioflavonoids implicated various disorders.

PHARMACOLOGICAL ACTIVITY OF BIOFLAVONOIDS

Antioxidant activity of Flavonoids.

Antioxidants are substances that when present in low concentrations, compared to those of an oxidisable substrate significantly delay or prevent oxidation of that substance[6].when the free radicals are generated during the metabolism and other activities beyond the antioxidant capacity of a biological system gives rise to oxidative stress[7]. Further oxidative stress plays a vital role in neurodegenerative diseases, heart diseases, in cancer and in ageing process [8]. Therefore, the Flavonoids have the free radical scavenging activity, which can help in oxidative stress.

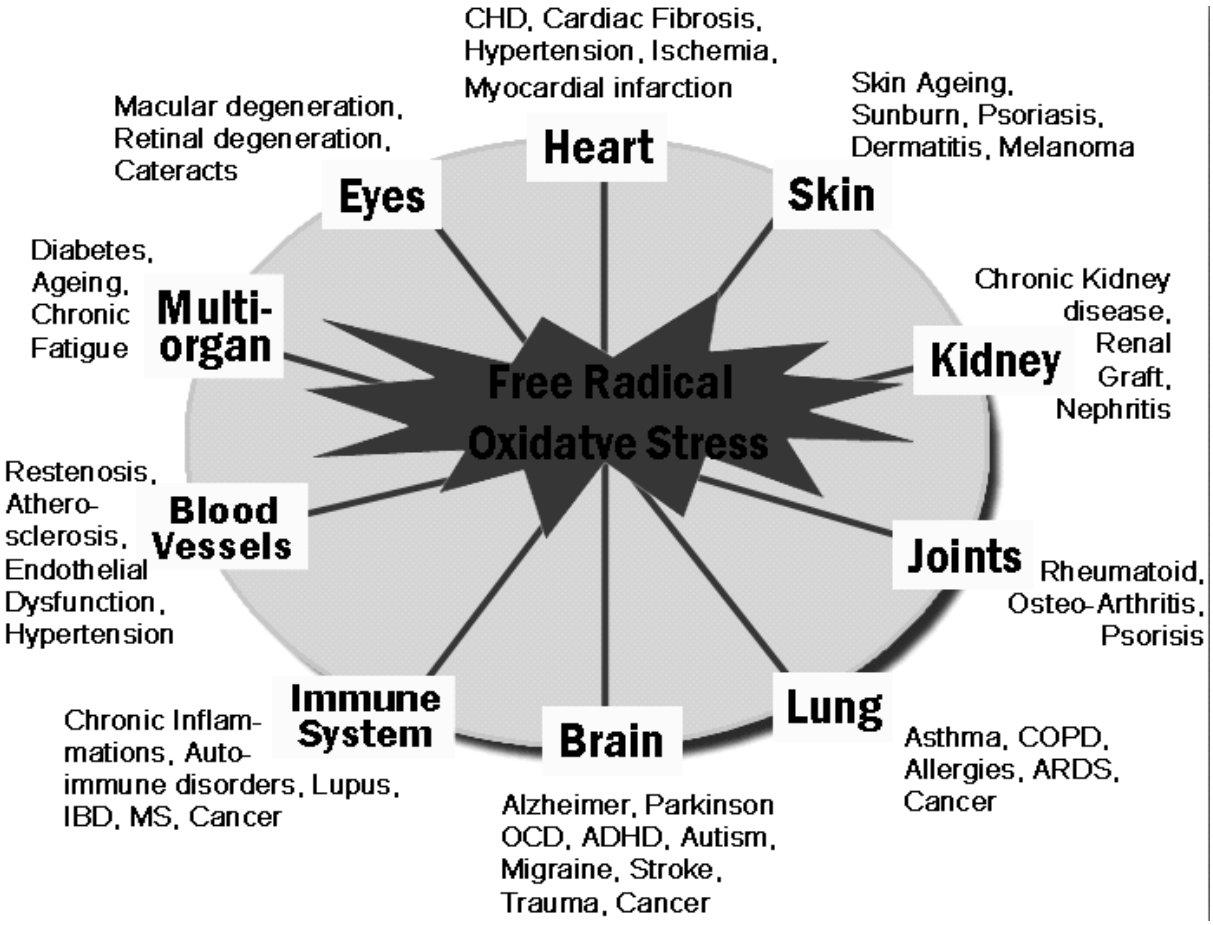

Fig 1: Effect of oxidative stress on different organs.

POTENTIAL HEALTH BENEFIT ON VASCULAR DISEASES:

Cardiovascular diseases are the basic cause of mortality .Bioflavonoid has been found to have therapeutic efficacy against various vascular disease. It has been found that Red wine and purple grape juice enhances platelet and endothelial production of nitric oxide (NO) [10, 12]. Moreover, the consumption of purple grape juice by the patients offered increased protection against low-density lipoprotein (LDL) cholesterol oxidation [13]. This indicate the role of flavonoids present in purple grape juice and red wine have the capacity to inhibit the initiation of the atherosclerosis. Further, they also have been found to possess strong antioxidant activity [14]. Bioflavanoid present in Apple peels were also shown to more effectively inhibit the growth of HepG (2) human liver cancer cells more effectively thereby indicating their potential in anticancer activity.

Flavonoids have been reported to exert their beneficial effect on the heart. 3-methyl quercetin has positive chronotropic effect on guinea pig right atrium and antiarrhythmic effect on left atrium [15]. In recent report the cardiotoxicity (negative inotropic effect) of doxorubicin on the mouse left atrium has been inhibited by flavonoids,7-monohydroxy ethyl rutoside and 7,1,3',4'-trihydroxyethyl rutoside. In a recent review, Huesken et al. gave detailed discussion on the cardio protective effects of Flavonoids. [16]

CNS activity of Bioflavonoids: Anti-inflammatory: A number of Flavonoids are reported to possess anti-inflammatory activity. Hesperidin, a citrus Flavonoid possesses significant anti-inflammatory and analgesic effects [17]. Recently, a new category of bioflavonoid apigenin, luteolin and quercetin have been reported to exhibit anti-inflammatory activity. It has been reported that hydroalcoholic extract of Phyllanthus caroliniensis possess antinococeptive action, which is, attributed

to the presecnce of quercetin, gallic acid ehyl estersand other unidentified Flavonoids in the extract. Treatment with silymarin demonstrated reversal of the carrageenin induced biochemical changes. Detailed biochemical studies to establish mechanism of action of Flavonoids have been carried out [18].

Anticonvulsant

Gossypin another important bioflavonoid has show good anticonvulsant activity. This effect was studied by inducing seizures by pentelentetrazol, strychnine, and maximum electroshock convulsive methods in mice. Gossypin seemed to reduce tonic extensor seizures induced by pentelenetetrazol [19]. It acts on GABA aminergic and glycine and hence inhibit them, this seems to be there probable mechanism of action [20].

MISCELANEOUS

Antimicrobial:

Flavonoids and esters of phenolic acids were investigated for their antibacterial, antifungal, and antiviral activities. All samples were active against the fungal and gram-positive bacterial test strains and most showed antiviral activity [21].

Antibacterial:

Bioflavonoids have shown remarkable antibacterial activity. Twenty-five bioflavonoids have shown antibacterial activity of all the bioflavonoid discovered till now. Most of the flavonones having no sugar moiety showed antimicrobial activity whereas none of the flavonols and flavonolignans tested showed no inhibitory effect on microorganisms. Compounds like myricetin deoxyhexoside, quercetin-3-o-glucoside and quercetin deoxyhexoside are said to possess antibacterial activity ($p<0.10$) at 80mg/kg in mice [22].

Antiviral Activity:

Bioflavonoids have shown antiviral activity and they also showed good results against HIV. It has been found that flavonols are more active than flavones against herpes simplex virus type 1 and the order of importance was galangin > kaempferol >

quercetin[23]. Recently, a natural plant flavonoid polymer of molecular weight 2100 Daltons was found to have antiviral activity against two strains of type-1 herpes type simplex virus, including a thymidine-kinase deficient strain and type -2 herpes simplex viruses [24]. Out of twenty-eight Flavonoids tested, flavan-3-o1 was more effective than flavones and flavonones in selective inhibition of HIV-1, HIV-2 and similar immunodeficiency virus infections [25].

BIOSYNTHESIS OF FLAVONOIDS:

There also is a growing understanding of the diverse physiological functions of these compounds in plants and their effects, both beneficial and detrimental, when consumed by mammals. This has led to the current understanding of the biosynthesis of the bioflavonoids . Due to the recent discoveries in deciphering the signaling pathways that regulate the expression of the flavonoid gene as well as mechanisms controlling the intracellular distribution of flavonoid end products [26, 27, 28]. In addition, the first three-dimensional structures of several flavonoid enzymes were solved in the past few years, first for CHS and CHI from Medicago truncatula, solved by Noel's group [29,30] and then for anthocyanidin synthase [(ANS) also known as leucoanthocyanidin dioxygenase (LDOX)] from Arabidopsis .

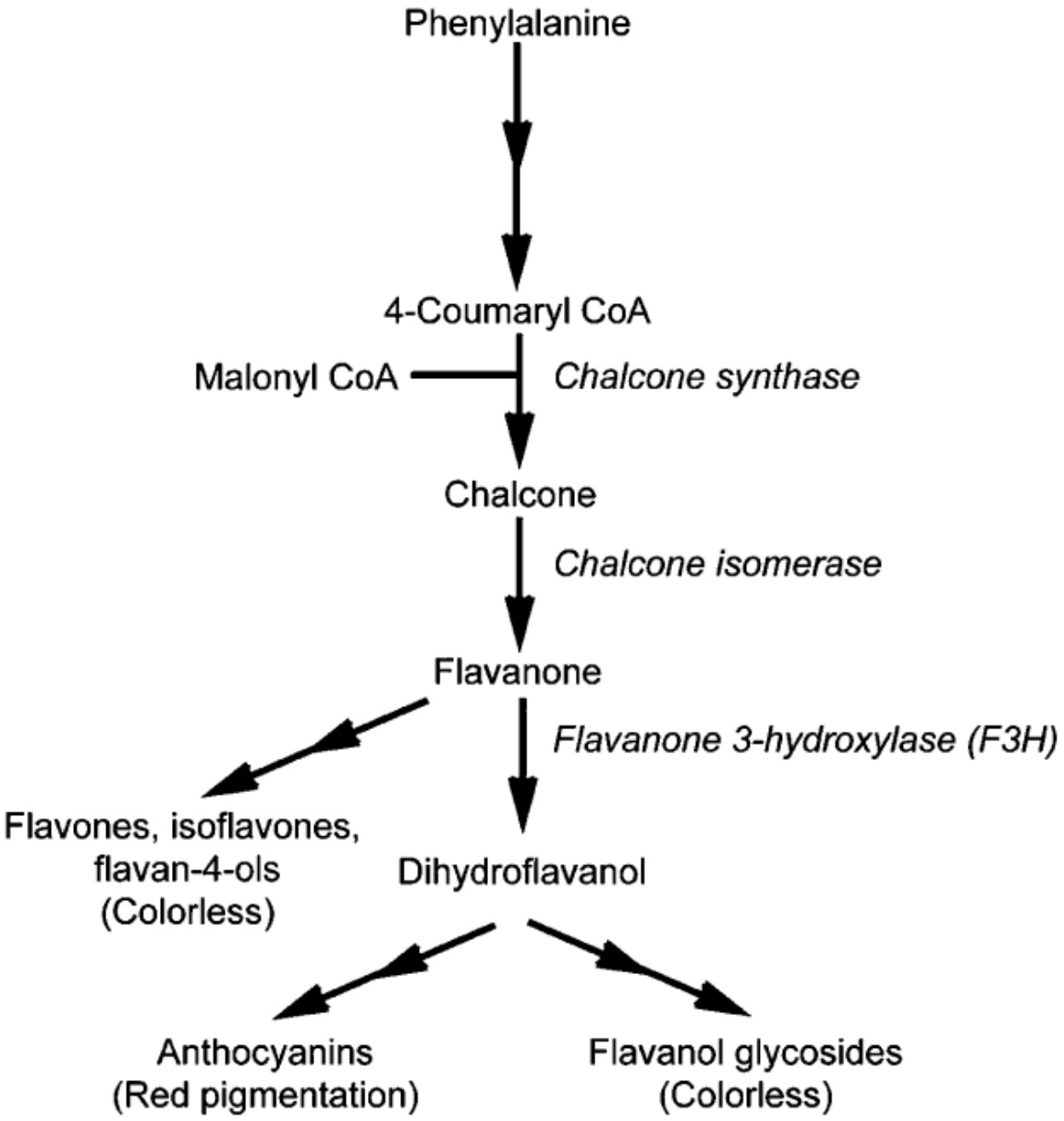

Fig 2: Biosynthesis of Flavonoids

BIOFLAVONOIDS AS SIGNALING MOLECULES:

A number of reports in the pharmacological literature have shown flavonoid interaction with cellular components implicated in neurological pathologies and cancer. Moreover, flavonoid seems to mimic endogenous mammalian receptor ligands [31, 32] and interfere with the uptake of substrates

not found in plants. However, the applicability of such studies to plant models needs several precautions. The studies of pharmacological Flavonoid function in animal cell often provide useful insights into their functions as signal molecules in plants. Almost every possible class of flavonoid has some pharmacological activity and most of them related to antioxidant activity. In most of the plants flavonoid appear to contribute to a general reduction of reactive oxygen species and thus affect the processes sensitive to redox effects. Flavonoids also have been implicated in more direct interactions with transport and signal transduction pathways. One well-documented example is the role of flavonoids in fertility: while a few flavonoid-deficient plants are able to germinate, grow, and set fertile seed most plants require flavonoids for fertility and normal pollen development. Moreover flavonoid specifically quercetin have been reported to inhibit (TNF alpha) transcription via inhibiting phosphorylation.

MOLECULAR TARGETS OF FLAVONOID ACTION:

At the molecular level, potential targets of flavonoid regulation in plants range from transcription factors and kinases to ATP-binding cassette (ABC) transporters and aminopeptidases. Some of these targets are suggested primarily by similarities between plant and mammalian signaling mechanisms. In animals, flavonoids interact with plasma membrane and cytosolic targets and some similarity exists between the moleculaar targets and planta this is an important feature of flavonoids. The best example of this is that potential pharmacological outcome for flavonoids is the ability to inhibit p-glycoprotien MDR1 an integeral membrane protien in mammals with similarity to plant auxin eflux protien [33]. Other molecular targets of Flavonoids include cyclooxygenase 2 (cox2), nitric oxide synthase (NOS), [34, 35] and the GLUT4 that mediated insulin dependent glucose uptake [36]. The potential new targets are given below.

TRANSCRIPTION:

Nuclear localization of flavonoids has been reported in many plant species, suggesting that flavonoids may function in transcriptional regulation of endogenous gene expression. Reports of sulfonated flavonols in nucleus in Flaveria chloraefolia, [37] and unidentified phenolic compounds in Brassica napus also were localized in the nucleus but not nucleolus [38]. Nuclear localization of flavonols also has been shown in Arabidopsis thaliana [39, 40] and flavanols in Tsuga canadensis, Taxus baccata, Metasequoia glyptostroboides, Coffea arabica, Prunus avium, and Camellia sinesis [41]. Catechin binding of histone proteins has been demonstrated in plants [42] suggesting that catechins might modulate nonspecific gene transcription. Naringenin chalcone and apegenin can also influence flavonoid biosynthesis by regulating transcription of flavonoid biosynthetic enzyme [43].Recently it has been shown that flavonoid biosynthetic enzymes chalcone synthase(CHS) and Chalcone isomerase (CHI) are localized in the nucleus and as well as cytoplasm, in A.thaliana suggests that flavonoid regulation if transcription is regulated at the sub cellular level[44]. This observation is also seen in phenolics in sub cellular compartments observed throughout seed development and germination [45]. Pharmacological studies of flavonoid effects on mammalian transcription suggest other potential sites of regulation in plants. Quercetin inhibition of histone H1 and H2AX phosphorylation and genistein inhibition of H2AX phosphorylation has been documented [46]. Glucopyranosides of kaempferol and quercetin also specifically bind DNA polymerase α in vitro [47] however, in vivo binding and subsequent transcriptional induction or repression has not been shown. Flavonoids also may affect transcription by inhibiting topoisomerase (topo) activity: quercetin, myricetin, fisetin, and morin inhibited both topo I and II activity, while kaempferol, phloretin, and apigenin specifically inhibited topo II [48], and quercetin, kaempferol, and naringenin

stabilized the topo II-DNA complex [49]. Most of the regulation of transcription by flavonoids appears to involve inhibition of phosphorylation signaling cascades or specific kinases. Quercetin specifically inhibited tumor necrosis factor α (TNFα) transcription through inhibition of phosphorylation of c-Jun N-terminal kinase/stress activated protein kinase (JNK/SAPK), thereby suppressing activator protein-1 (AP-1) from binding to TNFα promoter [50].Apigenin inhibited inhibitor κB kinase (IκB) activity, thereby inhibiting nuclear factor κB (NF-κB)- dependent COX-2 transcription [51]. The flavonols kaempferol and quercetin inhibited transcription factor AP-1 activation of nitric oxide synthase expression while the isoflavone genistein did so via NF-κB inhibition [52]. Quercetin inhibited an AKT/protein kinase B (PKB) and extracellular signal-related kinase (ERK) phosphorylation and also activated Quercetin activated transcription of heme oxygenase-1 via mitogen-activated protein kinase (MAPK) signaling cascade, but inhibited ERK [53]. Apigenin inhibited expression of vascular endothelial growth factor and hypoxiainducible factor-1α via PIPK/AKT and HDM2/p53 (which regulates MAPK) pathways [54]. Apigenin also has been shown to inhibit Ras signaling.

Secreted NOD factors (*N*-acetylchitooligosaccharides) also alter apoplastic pH and initiate a Ca2+ cascade, which is thought to either initiate or repress defense responses in the plant [55]. Nodulation is initiated when the bacteria invade the root and is completed when a vascular bundle is formed in the nodule. Auxin accumulates during early nodule formation and is thought to result from flavonoid inhibition of auxin transport to the root tip [56]. Flavonoids also likely regulate localized auxin concentrations within the nodule: 7,4′-dihydroxyflavone and its derivative inhibited IAA breakdown, while formontonin, an isoflavone, enhanced it [57] The process of rhizobial nodulation is not similar to lateral root formation, as cortical

cell proliferation occurs followed by vasculature formation in the nodule.

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