Pharmacognosy Reviews
Vol 1, Issue 1, Jan-May, 2007

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PHCOG REV.: Review Article

Flavonoids: A Nutritional Protection against oxidative and UV induced cellular damages

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ABSTRACT

Bioactive compounds and establishing their health effects are active areas of scientific queries. There are exciting prospects to facilitate the selection of many bioactive compounds, which are supportive to reduce the risk of many diseases, as well as chronic diseases such as cardiovascular disease. This review provide an summary of activities of bioactive components like flavones, flavonols, catechins, anthocyanidins (e.g., cyanidin, pelargonidin), and isoflavones (e.g., genistein, daidzein & proanthocyanidins (Polymeric flavonoids), Glucosinolates & isothiocyanates. Such bioactive components impart potential role in enzyme biology (enzyme modulator activities) and in straight line or indirect act as antioxidant, anti-inflammatory, and protection against ultraviolet light induced damages, which affects the health. The number of bioactive compounds and the diversity of likely biological effects, numerous and diverse experimental approaches must be taken to increase our understanding of the biology of bioactive compounds. The discovery of novel health effects of bioactive compounds will provide the scientific basis for future efforts to use biotechnology to modify and make stronger food components as a means to improve public health.
KEYWORDS: Flavonoids, Bioactive Enzyme, UV, Antioxidants, cellular damages

INTRODUCTION

Nutrition is an era of alteration, which defined the role of bioactive compounds present in the foods materials. These compounds are defined as components of foods that influence physiological or cellular activities resulting in a beneficial health effect. This definition distinguishes these compounds from many others that are bioactive, but have detrimental effects and are considered as toxic e.g. few plant secondary metabolites. Nutrient classifications (1-7) are shown in (Table 1). The purpose of this review is to provide an overview of the scientific evidences to straighten out the biological and a health effect of these bioactive compounds above all flavonoids (quercetin, kaempferol, myricetin etc.) one of the groups, which plays diverse role in different way in our biological system. These compound are typically occur in small amounts in different foods (8). Intrinsically, bioactive compounds have more delicate effects than nutrients. For example, polyphenolic compounds which influences cellular activities in different ways and modify the risk of disease, rather than prevent deficiency diseases.

The current focus on the potential and beneficial role of these bioactive compounds in several chronic diseases, there is intense disclose interest in studying the health effects of bioactive compounds and sorting out the mechanisms that mediate their effects. The primary challenge in this area is to identify bioactive compounds and their associated health effects as well as their underlying biological mechanism of action. An impressive and growing number of bioactive compounds have been identified that have potentially important health benefits via distinguished mechanism actions and can act as antioxidants, enzyme inhibitors and inducers, inhibitors of receptor activities, and inducers and inhibitors of gene expression, photo protective among other actions.

Demonstration of these activities as alone is not sufficient for a compound to be defined as a bioactive; it also must have an associated beneficial health effect. Another important peculiarity of such compounds is that unlike nutrients, which generally have very specific functions such as being an enzyme cofactor, bioactive compounds also may have overlapping functions or activities such as antioxidant activities, wherein multiple compounds may perform the same function or have similar activities. The number and diversity of bioactive compounds adds much complexity to understanding their effects on health. Here we tried to pull together some activities of major flavonoids, which are proved scientifically at cellular level laboratory research studies.

Flavonoids are nearly ubiquitous in plants and are recognized as the pigments responsible for the colors of leaves, especially in autumn. They are rich in seeds, citrus fruits, olive oil, tea, and red wine. They are low molecular weight compounds composed of a three-ring structure with various substitutions. This basic structure is shared by tocopherols (vitamin E).

CHEMISTRY OF FLAVONOIDS

More than 5000 different flavonoids have been described. The six major subclasses of flavonoids include the flavones (e.g., apigenin, luteolin), flavonols (e.g., quercetin, myricetin), flavanones (e.g., naringenin, hesperidin), catechins or flavanols (e.g., epicatechin, gallocatechin), anthocyanidins (e.g., cyanidin, pelargonidin) and isoflavones (e.g., genistein, daidzein) (9). Flavonoids are the largest class of polyphenols, with a common structure of diphenyl propanes (C6-C3-C6), consisting of two aromatic rings linked through three carbons

(Figure 1). Biogenetically, the A ring usually arises from a molecule of resorcinol or phloroglucinol synthesized from the acetate pathway and has a characteristic hydroxylation pattern at the 5 and 7 position (10).

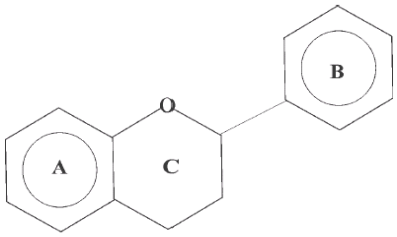


Figure: 1 Basic flavonoid structure

The B ring comes from the shikimate pathway and is usually 4, 3, 4-, or 3,4,5-hydroxylated. Based on their chemical structure, flavonoids are divided into several subclasses (subclasses, specific compounds, and major food sources. Table 2), of which flavonols are the most abundant in the plant kingdom (11).

Flavanols*:*Tea (green and black), red wine and chocolate are the foremost sources for flavanols like catechins. Grape and chocolate catechins are mainly (C)-catechin and epicatechin (EC), while tea catechins also have galloyl esters of catechins as major components. Proanthocyanidins are polymeric flavanols (4 to 11 units) that are present in plant materials such as grape seeds. Red wine contains more flavonoids (resveratrol found to be inhibit AOM-induced colon tumorigenesis) than grape juice because the winemaking process extracts some of the flavonoids from the seeds and skins of grapes.

Flavonols:

Quercetin is the main flavonol in the human diet, present in many fruits, vegetables and beverages. It is particularly abundant in onions (0.3 mg/g fresh weight) and tea (10–25 mg/L). Quercetin usually occurs as *O*-glycosides, with D-glucose as the most frequent sugar residue. More than 170 different quercetin glycosides have been identified.

Isoflavones:

Soybeans are the only significant dietary source of isoflavones. The primary isoflavones in soy are genistein and daidzein (approximately 1 mg/g dry bean), which are generally considered as phytoestrogens.The flavonoid consumed most was quercetin, and the richest sources of flavonoids consumed usually via tea (48% of total), onions, and apples (12). A rebirth of interest in traditional eastern medicine during the past two decades, together with an expanded effort in pharmacognosy, has rekindled interest in the flavonoids and the need to understand their mechanism and effects at the cellular level. Flavonoids have important effects in biochemistry and physiology, acting as antioxidants, enzyme inhibitors, precursors of toxic substances, and pigments and light screens, which are also, play significant role in UV rays protection.

The flavonoids have long been recognized to possess anti-inflammatory, antioxidant, antiallergic, hepatoprotective, antithrombotic, antiviral, and anticarcinogenic activities (13-15), are summarized in Table.3. These typical phenolic compounds act as potent metal chelators, free radical scavengers and display a remarkable collection of biochemical and pharmacological activities (*In-vitro*) of many enzymes system (16).

MECHANISM

Other multitude effects of mass of flavonoids upon enzyme systems directs an influence on immune cell function via different mechanism are as followed.

- Suppression of Class II histocompatibility antigens in peripheral blood monocytes (56).
- Inhibition of lymphocyte proliferation in response to phytomitogens and antigens (57).
- Inhibition of thymidine transport in lymphocytes (58).
- Effects on tumor cell immunity (Flav's cause enzymatic alterations in tumor cells) (59).
- Stimulation of IgE formation (60).
- Inhibition of cytotoxic lymphocyte formation (61).
- Inhibition of cell proliferation (62).

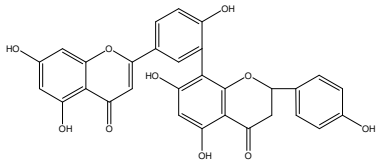
As antioxidants:

Antioxidants are compounds that protect cells against the damaging effects of reactive oxygen species, such as singlet oxygen, superoxide, peroxyl radicals, hydroxyl radicals and peroxynitrite. An imbalance between antioxidants and reactive oxygen species results in oxidative stress, leading to cellular damage. Oxidative stress has been linked to cancer, aging, atherosclerosis, ischemic injury, inflammation and neurodegenerative diseases (Parkinson's and Alzheimer's). Many flavonoids may help to provide protection against these diseases by contributing, along with antioxidant vitamins and enzymes, to the total antioxidant defense system of the human body. Epidemiological studies have shown that flavonoid intake is inversely related to mortality from coronary heart disease and to the incidence of heart attacks. From the above table we can assure that variety of flavonoids act in different way to control the oxidation at the cellular level as antioxidants by interfering in enzyme activity, chelating of redox-active metals and by scavenging free radicals.

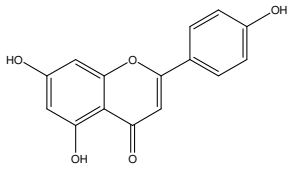
Chelation of both iron and copper by the carbonyl and hydroxyl groups of flavonoids prevents peroxyl radical and lipid peroxidation (63, 64). Here flavonoids also act as terminators of free radicals by donation of electrons to form stable products. Flavonoids are very effective scavengers of hydroxyl and peroxyl radicals as well as quenching superoxide radicals and singlet oxygen (65).

In case of atherosclerotic lesions, oxidation of low-density lipoproteins (LDL) is considered to be a very important component (66, 67). The antioxidant mechanism during the atherogenesis is clearly shown in the figure 2. In blood circulating monocytes scavenge oxygen-modified LDL molecules and monocytes/macrophages penetrate into the sub endothelial space and become the first stage of atherogenesis, the so-called "fatty streak." Flavonoids, with antioxidant activity interrupt this process and may be very helpful in the process of preventing and or treating cardiovascular diseases.

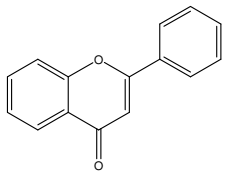
Ame ntoflavone



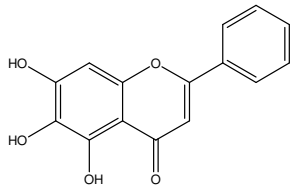
Apigenin



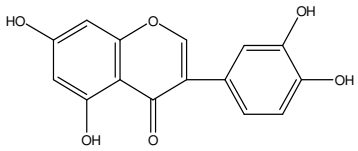
7, 8- benzoflavone



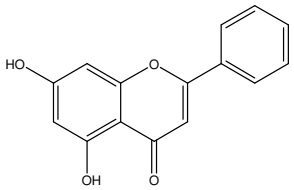
Baicalein



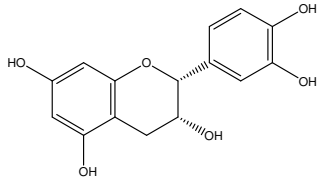
Apigenin



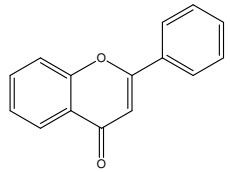
Chrysin



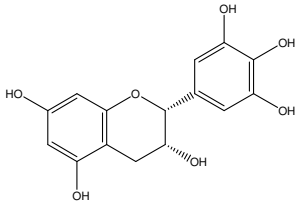
Epicatechin



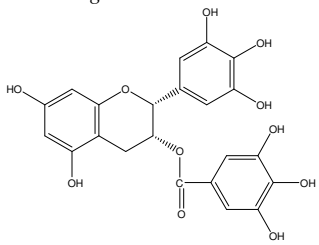
Epicatechin gallate



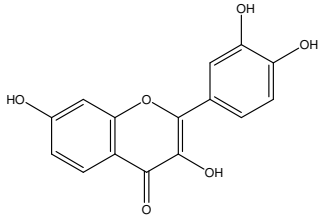
Epigallocatechin



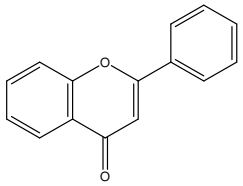
Epigallocatechin gallate



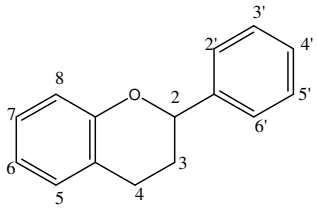
Fisetin



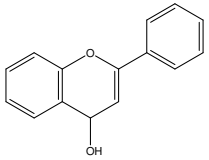
Flavone



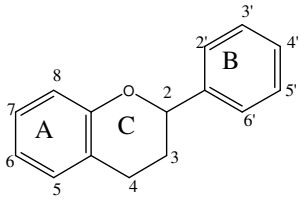
Flavonoids



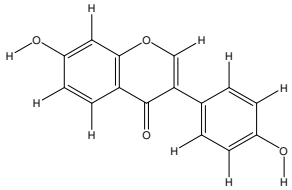
Flavonol



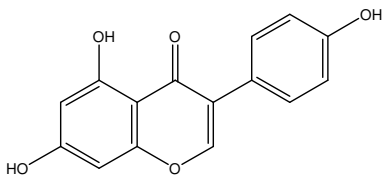
Flavonoxanthone glucoside



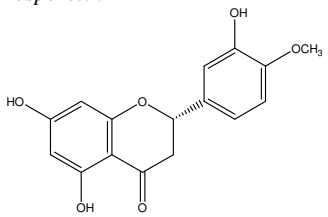
Diadzein



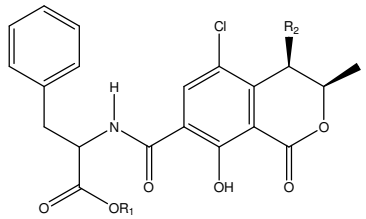
Genistein



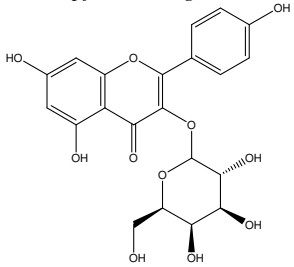
Hesperetin



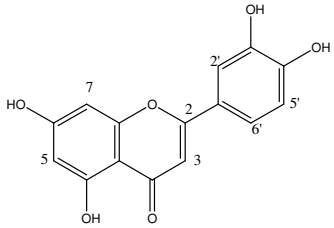
Isoflavones and 13 coumarins



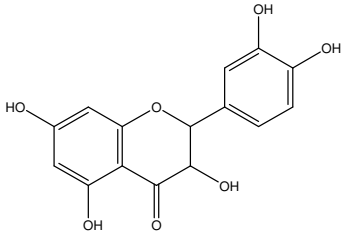
Kaempferol-3-O-galactoside



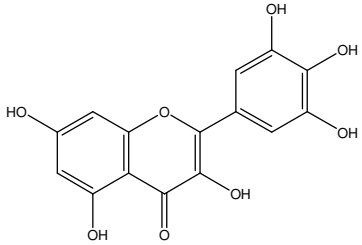
Luteolin,



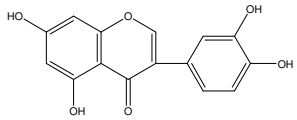
Taxifolin



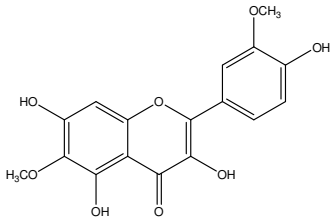
Myricetin



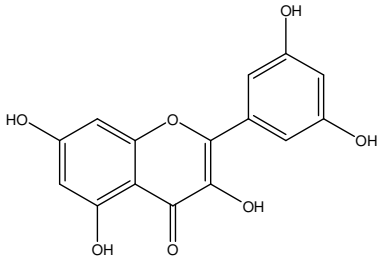
Prunetin



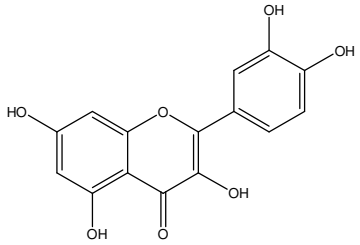
Quercetagetin



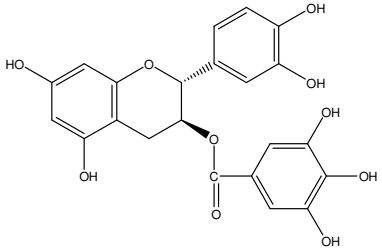
Quercetagetin-7-glucoside



Quercetin



Epigallocatechin gallate



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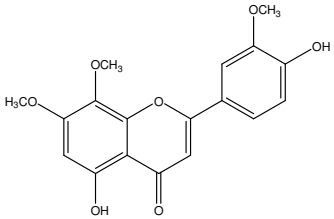
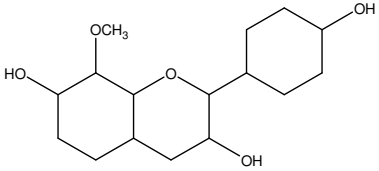
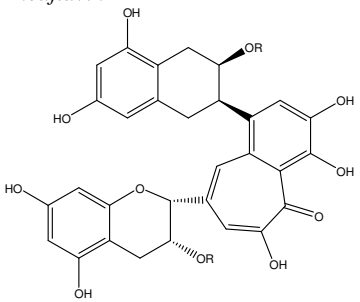
Scutellarein



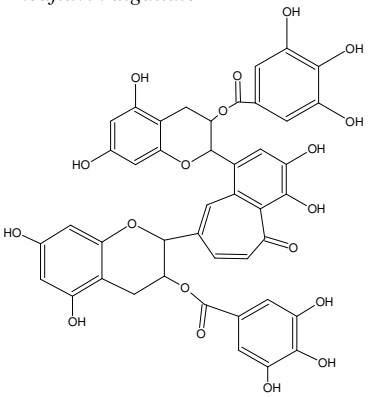
Tambuletin



Theaflavin

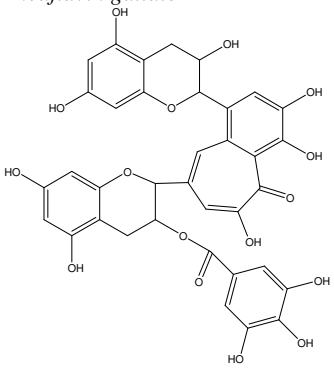


Theaflavin digallate



Naringenin

Theaflavin gallate



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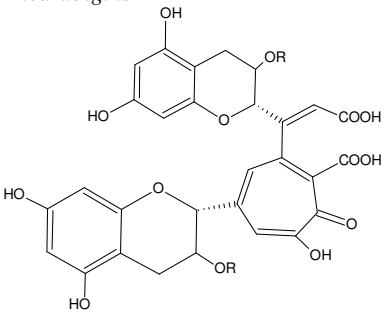
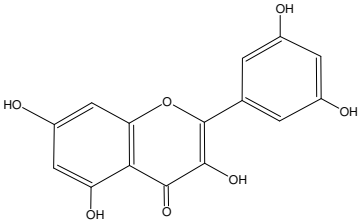
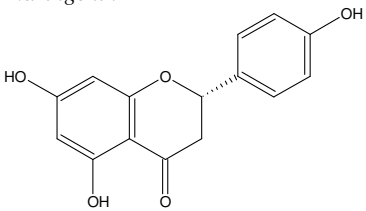


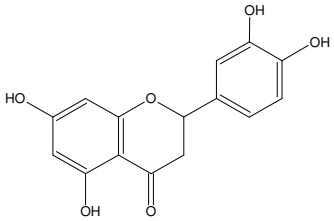
Morin



Naringenin



Eriodictyol



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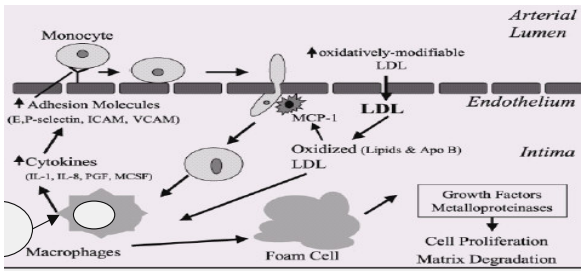

Figure. 2 - An Oxidative modification pathway via Low-density Lipoprotein accumulation.

Mechanism of oxidation

Oxidized LDL triggers a cascade of proatherogenic events (Figure 1). In this local vascular cells are stimulated by oxidized LDL to produce monocyte chemotactic protein 1 (MCP-1) and granulocyte and macrophage colony-stimulating factors that promote recruitment of monocytes to the endothelium and uptake, followed by conversion to macrophages in the arterial wall (68). In conjunction with this, a cytokine-induced [tumor necrosis factor *a* (TNF-*a*) and interleukin-1 (IL-1)] expression of endothelial cell surface adhesion molecules stimulates recruitment of blood mononuclear cells to the endothelium. Accumulating monocytes and macrophages further stimulates LDL oxidation (69).

The mechanism by which flavonoids inhibit LDL is not totally known, but it is thought that they reduce free radical formation, protect LDL- *a* -tocopherol or regenerate oxidized LDL- *a* -tocopherol, and/or sequester metal ions which participate in oxidation reactions (70). The flavon 3-ol, catechin and silybin found to be effective in liver toxicity which is induced from drugs such as erythromycin estolate, amitriptyline, nortriptyline, and *tert*-butylhydroperoxide, the hepatotoxicity were found decreased by catechin and silybin flavonoids (71).

As Anti-inflammatory

Green tea, black tea, plums, apples, and cranberries contained supplement of Flavan-3-ols (Catechin, gallocatechin, epicatechin, epigallocatechin, epicatechin gallate, epigallocatechin gallate, theaflavin, the aflavin gallate). Some of these flavonoids have anti-inflammatory properties, probable by inhibiting the production of TNF-*a* and nitric oxide.

Suppression of the inflammatory response in chronic diseases may beneficially affect disease outcome. During the inflammation the Intercellular adhesion molecule (ICAM)-1 plays an important role in the inflammatory responses. Expression of ICAM-1 is induced by cytokines, such as IL-1, TNF-*a*, or INF-*y*, on endothelial cell surface during inflammation. Quercetin inhibited ICAM-1 expression induced by phorbol 12-myristate 13-acetate and TNF-*a* in ECV304 human endothelial cell in a dose dependent manner (72). This inhibition was due to down regulation of activator protein-1 that is associated with inhibition of c-Jun NH2-terminal kinase pathway. In another study, apigenin exhibited a dose- and time-dependent inhibition of cytokine-induced ICAM-1, VCAM-1, and E-selectin expression. In this study, apigenin did not inhibit nuclear translocation of NF-κB, but did inhibit reporter gene expression driven by NF-κB (73).

Flavonols, quercetin and catechin were found to inhibit the production of TNF-*a* and nitric oxide by lipopolysaccharide-activated macrophages (74). TNF-*a* inhibition may occur post transcriptionally whereas inducible nitric oxide synthase inhibition may occur at the transcriptional level (75).In lipopolysaccharide activated Kupffer cells, quercetin also strongly inhibited nitric oxide production and TNF-*a* expression, possibly through a posttranscriptional process. Quercetin is reported to suppress TNF-*a*-induced expression of IL-8 and monocyte chemo attractant protein (MCP)-1 due, at least in part, to its ability to inhibit the activation of NF-κB (76). Similarly, apigenin, one of the most potent flavones, inhibits prostaglandin synthesis induced by IL-1*a*. Apigenin also inhibits the production of IL-6 and IL-8 in human endothelial cells activated by TNF-*a* (77).

As Photo protective

Skin ages in a sequential logic with impaired cellular and subcellular functions are natural phenomenon. On the other hand, skin may also age prematurely as a result of overexposure to exogenous environmental factors for example UV radiation, smoking effect (78). This photo aging process is mainly related to increased exposure to UVA light, but UVB also initiates photo aging, which altered the skin extra cellular matrix of collagens (79). As an outcome of skin loses, rigidity, elasticity, and resilience, are appearing rough, leathery, and wrinkled (80).

There are different strategies for protection of skin against UV-dependent damage (81). Most simple are avoidance of sun exposure and wearing protective clothing as well as topical application of sunscreens, generally recommended during times of intense exposure, e.g., during holidays or stays at high altitude. It has been speculated that an increased topical protection against UV light might affect endogenous vitamin D synthesis in the skin and may cause disorders related to vitamin D deficiency, e.g., reduced bone strength (82, 83). On the other hand, at present the intake of a vitamin D supplement during use of a sunscreen is discussed controversially (84).

Human skin is protected against UV radiation by melanins, endogenous pigments that scatter and absorb UV light (85).Upon sun the exposure; pigmentation is enhanced by stimulated synthesis of melanin in the epidermal melanocytes (suntan) and a cascade of photo-induced chemical and biological reactions takes place in the target tissue (86-88). As a primary event, light interacts with a suitable chromophore. The chromophore may be damaged directly or may act as photosensitizer initiating subsequent chemical reactions. In the presence of oxygen, secondary reactive oxygen intermediates are generated. These reactive oxygen species (ROS) may damage molecules and cellular structures. The chemical reaction cascade leads to cellular biochemical

Table: 1. Bioactive components viability in food materials

S.No.	Bioactive components	Food sources	Ref.
1	Carotenoids	Green, orange, red, yellow fruits & vegetables	1
2	Flavonoids & proanthocyanidins (Polymeric flavonoids)	Fruits & vegetables, soy foods, legumes, tea, cocoa	2,3
3	Glucosinolates & isothiocyanates	Cruciferous vegetables	4
4	Phenolic acids (Caffeic acid and chlorogenic acids,p-cumaric acids)	Cereals, coffee, fruits & vegetables	5,6
5	Plant sterols (campesterol ß-sitosterol and stigmasterol)	Rice oil, soybean oil, tall oil	7

Table 2. Flavonoid subclasses, compounds and food sources.

S.No.	Subclass	Compounds	Primary food sources
1	Flavonols,	Quercetin, kaempferol, myricetin	Onions, apples, teas, berries, isorhamnetin olives, bananas, lettuce, Plums, red wine
2	Flavones	Luteolin, apigenin	Apples, celery, celeriac, Lemons, parsley, oregano, Lettuce, beets
3	Isoflavones	Genistein, diadzein	Soybeans, legumes
	Flavanones	Hesperetin, naringenin, eriodictyol	Oranges, grapefruits, lemons
5	Flavan-3-ols,	Catechin, gallocatechin, epicatechin, epigallocatechin, epicatechingallate, epigallocatechin gallate, theaflavin, Theaflavin gallate, theaflavindigallate, thearubigins	Green tea, black tea, plums, apples, cranberries

Table 3 Different enzyme modulator activities of Flavonoids.

Sl.No	Enzymes	Flavonoids	Mechanism	Ref.
1	Protein Kinase	Quercetin	Inhibited the phosphorylating activity of the Rous sarcoma virus-transforming gene.	17
			Inhibition of phosphorylase kinase and also of protein tyrosine kinase	18
		Kaempferol	Catalyzes the Myosin light chain kinase (MLCK)	19
		Genistein	Inhibition of protein tyrosine kinases (PTK)	20
		Fisetin	Inhibition of nonactivated phosphorylase kinase	
2	Phospholipase A2 (PLA2)	Quercetin	Inhibition of PLA2 from human and rabbit leukocytes.	21
		Quercetagetin, kaempferol-3- *O*-galactoside, and scutellarein	Inhibition of human recombinant synovial PLA2	22
	Phospholipase C (PLC)	Genistein	Blocking the PLC activation and formation of inositol trisphosphate (IP3) and diacylglycerol (DAG).	23
3	ATPases	Quercetin	Mg 21-ectoATPase of human leukocytes.	
			Increase in ATPase activity by conformational changes in the structure of myosin.	24 25
4	Lipoxygenases and Cyclooxygenases	Quercetagetin-7-glucoside Tambuletin	Effect on arachidonic acid metabolism via the LO and CO (TxB2, PGE2, 6-keto-PGF1a) pathways.	26
5	Glucuronyltransferase	Catechins	The simultaneous induction of CYP1A2 and UGT activities.	27
7	Adenylate Cyclase	Prunetin, Apigenin	Inhibition of adenylate cyclase and decreased the platelet cyclic AMP response to prostacyclin	28
8	Reverse Transcriptase	Amentoflavone, scutellarein and quercetin	Inhibition of three reverse transcriptases (RT)	29

9	Ornithine Decarboxylase (ODC)	Quercetin	Inhibit the stimulatory effect of TPA on ODC activity and exert regulatory effects on cell growth.	
		Apigenin	Effective, dose-dependent inhibitor of ODC activity and papilloma formation.	30
10	Topoisomerase	Genistein Fisetin and quercetin	Inhibition of mammalian DNA topoisomerase II. Increasing the DNA-enzyme complex in L1210	
		Baicalein, quercetagetin, and myricetin	cells and interfering with enzyme-induced DNA relaxation.	31 32
11	Glutathione S-Transferase (GST)	Quercetin	Inhibited to varying degrees by in vitro	33
12	Epoxide Hydrolase	Flavone and 7,8-benzoflavone	both stimulated epoxide hydrase activity, reduced the carcinogens .	34
13	Glyoxalase	Quercetin, fisetin, myricetin	Inhibition of glyoxalase I and helpful in regulation of cell division.	35
14	Xanthine Oxidase	Quercetin Baicalein	Inhibitory action on both xanthine oxidase and xanthine dehydrogenase activity and reduced brain tumor	36. 37
15	Aromatase	Quercetin, chrysin, apigenin, kaempferol	By binding to the active site human cytochrome P450 aromatase. Inhibit the aromatase enzyme activity competitively in a human Glyoxalase cell culture system.	38 39
16	Cyclic Nucleotide Phosphodiesterase	flavone, flavonol	Inhibition of phosphodiesterases activity and involved in regulation of many cellular processes, such as cell division.	40 41
17	Catechol-O-methyltransferase	Certain flavonoid	Inhibition of the catecholamine-metabolizing enzyme catechol-*O*methyltransferase (COMT)	42
18	Aldose Reductase	Isoflavones and 13 coumarins	Activity against this enzyme	43
19	Monoamine Oxidase	Coumarins ,neoflavonoids	Inhibit monoamine oxidases A and B in a reversible a time-independent Manner	44
20	Hyaluronidase	Kaempferol	Tumor cell inhibition by breaking glucosaminidic bor	45
21	Histidine Decarboxylase	Quercetin and (1)-catechin	Inhibited the activity of histidine decarboxylase was inhibited	46
22	Human DNA Ligase	Flavonoxanthone glucoside	Inhibited enzyme function of DNA ligase I, which catalyzes the covalent joining of singl stranded breaks in doublestranded DNA	47
23	Aldose Reductase	Quercitrin	Inhibit the accumulation of sorbitol in the lens of the rodent	48 49
24	HIV-1 Proteinase	Myricetin, morin, quercetin, and fisetin	Replication of HIV-I inhibited by inhibiting enzyme activity.	50
25	HIV-1 Integrase	Quercetin,	Replication of HIV-I by inhibiting enzyme activity.	51
26	Nitric-Oxide Synthase	Quercetin, epigallocatechin gallate, morin, apigenin, taxifolin, fisetin, and catechin	Inhibit NO synthase isomer enzymes activity	52-55

Abbreviations:
AOM: Azoxymethane, EC: Epicatechin, MLCK: Myosin light chain kinase, PTK: Protein tyrosine kinases, PLA2: Phospholipase A2, IP3: Inositol trisphosphate, DAG: Diacylglycerol , ODC: Ornithine Decarboxylase, OPCs: Oligomeric proanthocyanidins, MAPK:Mitogen activated Protein kinase

responses including modified gene expression, impact on kinase-dependent signaling pathways, immune and inflammatory events, or induction of apoptosis.

Systemic photoprotection through endogenous supply of components provides an important contribution to the defense against UV effects. In addition to some drugs like

psoralens or antimalarial agents, dietary constituents have been investigated.

The polyphenols gained attention as protective agents against UV-induced damage. The most prominent phenolic compounds in green tea are the flavanols (-)-epigallocatechin, (-)-epigallocatechin-3-gallate, (-)-epicatechin, (-)-epicatechin gallate, (+)-gallocatechin, and (+)-catechin. Animal studies provide evidence that tea polyphenols, when applied orally or topically, ameliorate adverse skin reactions following UV exposure, including skin damage, erythema, and lipid peroxidation (89). Topical application of green tea polyphenols prior to exposure protects against UVB-induced local as well as systemic immune suppression; the effects established in vitro and animal models for photoprotection using other polyphenols and flavonoids have been investigated. In a mouse model, topically applied silymarin provided prevention against UV-induced skin tumors and found that silymarin lowered UVB-caused sunburn and apoptosis, skin edema, depletion of catalase activity, and induction of cyclooxygenase and ornithine decarboxylase activities as well as ornithine decarboxylase mRNA expression (97). Similar effects were reported for the flavonoid apigenin (98).

So like wise different bioactive compounds can interact in the dysfunction of the biological environment. The groups of scientist in research are identifying bioactive compounds and then establishing whether they have a beneficial health effect is gaining momentum. It is not unreasonable to speculate that important findings will be made that lead to new ways to exploit bioactive compound chemistry for the betterment of human health of population and make them safe from oxidative stress and UV radiations which has been linked to cancer, aging, atherosclerosis, ischemic injury, inflammation and neurodegenerative diseases (Parkinson's and Alzheimer's).

CONCLUSION

It is important to note that the different aspect of bioactive flavonoids focused in this review as antioxidants, anti-inflammatory agents and is complementary to topical photo - protection to maintain the biological environment of the skin and body at the cellular level. In future, such study claims can open the area of research for delivering such of micronutrients by designing novel protective formulations. While such studies require cumulative research that integrates various scientific disciplines, culminating in well-designed large intervention trials with the compounds of interest, which can be used as antioxidants. Further study of biokinetic, biochemical, and histological data are required for sound consideration for the development of food and cosmetic items enriched with micronutrients.

ACKNOWLEDGEMENT

Authors wish to thanks to the Head, National Medical Library, New Delhi and Head library of Pt. Ravishankar Shukla University, Raipur for providing literature facility, also thanks to Mr.Gopal Garg, lecturer, Institute of Pharmacy, Pt. Ravishankar Shukla University, Raipur for help in preparing the manuscript.

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