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MULTIFARIOUS ACTIONS OF DIETARY FLAVONOIDS – IMPLICATIONS IN CANCER AND CATARACT

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ABSTRACT

Flavonoids are widely present in fruits and vegetables. Different categories of flavonoids such as flavonals, flavones, flavonones, isoflavone, catechin, anthocyanin and isoflavone are present in plants. It has been discovered that they have many beneficial actions on body cells by enhancing the activity of many enzyme systems. The aim of this present review is to summarize the significant multifunctional and biological activities of flavonoids such as anti-allergic, anti-toxic, anti-microbial, anti-cataract and anti-cancer activity and to present the recent advancements in the pharmacological and chemical properties of flavonoids.

KEYWORDS: **Flavonoids, anti-cancer, quercetin, cataract and anti-microbial.**

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INTRODUCTION

Diverse beneficial effects of plants have been related to the presence of phytochemicals such as polysaccharides and flavonoids [1]. Flavonoids are bioactive polyphenols of low molecular weight [2, 3] that play an important role in photosynthetic plant cells[4]. Flavonoids are identified by their flavan nucleus[5] and carbon skeleton [6,7]. Until nearly 50 years ago, the mechanism of flavonoid action was not clear. Research in flavonoids began in early 1930s; Albert Szent- Gyorgi a Hungarian scientist, discovered a new substance from oranges. It was first termed as "Vitamin P". Later, it was clarified that this substance was " Rutin" (a Flavonoid), since then a great interest in flavonoids was evidenced. They possess a phenyl benzopyrene nucleus (C6-C3-C6) and are classified into different groups such as flavanols, flavones, isoflavones, flavones, and flavanonols based on their chemical structures [8, 9] (Table 1). It was discovered that the normal human intake of flavonoids is a few 100s of mg/day [10]. These compounds are widely present in medicinal plants and have been an important part of folk medicine globally in India and China [11 - 15]. These bioactive compounds showcase a significant spectrum of biological actions that include anti-cancer, anti-allergic, anti-mutagenic, anti-cataract, anti-toxic and the modulation of enzyme actions [16, 17]. This review article focuses on the multifarious actions of dietary flavonoids.

Table 1
Different subclasses of flavonoids and their sources [3, 18]

Sl.no	Sub-classes of flavonoids	Important flavonoids present	Source
1.	Flavonones	Naringen, Herpesitin	Citrus peels
2.	Flavonol	Quercetin, Rutin	Tea, Onion
3.	Catechins	Catechins, Epicatechins	Red wine, Tea, Fruits
4.	Isoflavones	Daidzen, Glycindin	Beans
5.	Flavones	Apigenin,Luteolin, Quercetin	Citrus fruit, Parsley
6.	Anthocyanidins	Cyanidin,Delphinidin, Malvidin	Grapes, apple skin, celery, Berries, Olives, grapes, Tea.

MULTIFARIOUS ACTIONS OF DIETARY FLAVONOIDS

I. Flavonoids and Carcinogenesis

Any disturbance in the growth metabolism leads to cancer [19]. The main contributing factors are inadequate anti-oxidant systems and the presence of high levels of ROS and free radicals [20, 21]. These ROS directly interfere with cell growth and signaling. The damage by ROS at cellular level induces mitosis and hence increases the chances of the damaged DNA to form mutations. Many studies have revealed potent anti-oxidants that suppress carcinogenesis . Studies involving fenugreek seed extracts proved to be potent anti-colon cancer agents by altering the expression of phospholipase A and by decreasing the levels of cholesterol[22]. Anti-tumourigenic activity of fenugreek seed extracts were also revealed in 1,2-dimethylhydrazine (DMH) induced wistar rats[23]. Flavonoids are effective bioactive compounds that can interfere with the progression of cancer by various modulations (Fig 1). Flavonoids such saponins were found to be significant inhibitors of cell proliferation [23]. Studies showed an inverse correlation between occurrence of lung cancer and intake of flavonoid quercetin. Studies in mice revealed the anti-metastatic capacity of apigenin and quercetin in mice [24]. Angiogenesis is a controlled process in the body, that is activated mainly during wound healing. Unregulated angiogenesis leads to carcinogenesis [25]. Flavonoids were found to interfere with the endothelial cell migration, protein kinase production and lumen formation and hence proved to be potential angiogenesis inhibitors [23, 26, 27]. Various research groups showed the *invitro* anti-cancer effect of various flavonoids on different cell lines (Table 2).

Table 2
Invitro anti-cancer effects of flavonoids

Sl.no	Type of cancer	Cell line used	Flavonoid	Reference
1.	Human lung cancer	A549, H441, H661, SW900	Quercetin, flavones	28 , 29
2.	Human oral cancer	HSC-2, HSG, SCC-25	Quercetin, chalcones	30-34
3.	Human thyroid cancer	ARO,WRO,NPA	Apigenin, kaempferol, catechin, luteolin,genistein	35, 36
4.	Human prostate cancer	DU145, PC3	Silymarin, myricetin, apigenin, luteolin, epicatechin, catechin	37-40
5.	Human breast cancer	MCF-7	Quercetin, luteolin, genistein	41, 42
6.	Human leukaemia	HL-60, K562	Quercetin, myricetin, apigenin, chalcones	43-46
7.	Human colon cancer	HCT-15, IEC-6,HT-29	Genistein, quercetin, anthocyanin	47-51
8.	Mouse melanoma cancer	4A5	Chalcones	52

2,4-Dimethoxybenzaldehyde (DMBA) induced cancer was inhibited by consuming dietary quercetin in hamster [53] and rats [54]. Studies by Khanduja *et al*., also revealed that ellagic acid and quercetin inhibited lung cancer in mice [55]. Quercetin inhibited tumour formation in the small intestine [56]. In animal models, rats fed with 0.05% of chalcone , 2-hydroxy chalcone or quercetin in diet prevented 4-Nitroquinoline-1-oxide (4NQO) induced cancer. Studies involving A/J mice (57) showed that lung tumours were inhibited by catechin rich tea. Investigations of 4-Methyl Nitrosamine-1-3, Pyridyl-1 Butanone (NNK) induced mice given black or green tea prior to the administration of the toxin significantly reduced the total number of tumours formed in mice. With intra-peritoneal administration of apigenin or quercetin, it was found that melanoma cancer was inhibited [29.] The preventive effect of apigenin was found to be due to the prevention of phosphorylation process of Mitogen Activated Protein Kinases (MAPK).

Pathway of carcinogenesis and the potential benefits of flavonoids

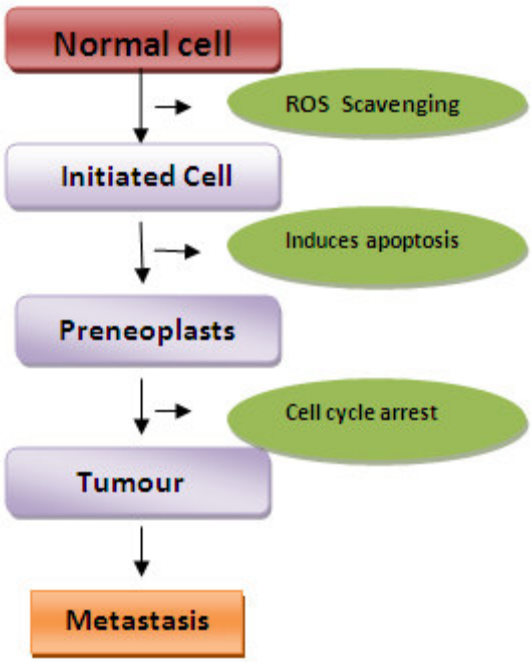

Figure 1
Pathway of carcinogenesis and the potential benefits of flavonoids [58]

II. Anti-Cataract Activity of Flavonoids

One of the major complications of diabetes mellitus is cataract. 60% of patients with diabetes are prone to this eye condition. The correlation between Diabetes and formation of cataract was discovered in many research studies [59]. The glucose from the extracellular region diffuses into the lens because of the uncontrolled action of the hormone insulin and hence leads to the formation of cataract. Cataractogenesis is a multi-functional process. It was recently found that many pharmacological actions of flavonoids can act in the inhibition of cataract. *Invitro* Studies using rat lens organ culture with hydrogen peroxide showed that small levels of quercetin prevented loss of transparency of lens induced by calcium and sodium influx [60]. Studies by Cornish *et al*., 2002, showed that quercetin and 3'-O-methyl quercetin (its metabolite) were responsible for preventing damage in the eye lens [61]. Cataract induced by the compound selenite was prevented by an isolated bioflavonoid (methylated quercetin) from *Cochlospermum religiosum* leaves [62], similarly the flavonoid from *Vitex negundo* leaves also protected rat eye lens from the cataract induced by selenite [63].Venorutun, decreased the extent of leakage of lactate dehydrogenase and opacification of rat lens hence reducing cataract effects [64]. *Invivo* Studies The selenite induced cataract model in rats was mainly used to study the anti-cataract effects of flavonoids [65, 66]. In streptozotocin induced rodents the effect of quercetin rhamnoside was studied early as 1977 [67]. The animals in the study did not develop cataract when treated with quercetin in contrast to the control animal. Similarly, isoflavone significantly reduced the prevalence of cataract and death in diabetic animals [68]. Studies involving a group of bioflavonoids and flavangenol showed the prevention of cataract in diabetic animals [69]. Studies on neonatal galactosemic rats involving topically applied quercetin on the orbital pouch showed reduced cataractogenesis in rat lens. Quercetin acted by inhibiting extracellular fluid and decreasing intracellular edema [70]. Similar studies by Mohan *et al*., showed the anti-cataract activity by topically applied myricetin and quercetin [71]. The flavonoid genistein decreased the development of cataract in rats induced by galactose in diet [72]. Studies by Isai *et al*., showed that rutin prevented cataract induced by selenite in rat pups [73]. Studies involving the instillation of crude onion juice into the eyes of rats were found to inhibit the formation of cataract by 75%. Onion was found to contain quercetin in the form of quercetin 3,4' – diglucoside and quercetin 4' – glucoside [74]. The onion juice was also found to increase the anti-oxidant enzyme levels in rat lens.

Isolated flavonoids from black and green tea [75], grape seeds, *Ginkgo biloba* [76, 77, 78], *Vitex negundo* [79] were also found to have anti-cataract action in experimental selenite induced cataract animal models. Radiation induced cataract was found to be inhibited in rats by *Gingko biloba* extracts [80]. The role of flavonoid, catechin as an anti-cancer agent was found in N-methyl- N nitrosurea induced cataract rat models [81]. Flavanoid rich grape seed extract decreased apoptosis of human lens cells induced by hydrogen peroxide[82]. UV-induced stress was prevented by flavonoid, fisetin by modulating the MAPK pathways [83]. Other Medicinal Properties of Flavonoids

III. Flavonoids and Thrombosis

Thromboxanes and endoperoxidases are formed from the metabolism of Arachidonic Acid (AA) that is formed during inflammation. This condition contributes to platelet aggregation and activation, which further leads to the formation of platelet thrombus and atherosclerosis. Studies in 1960's showed that coagulation of blood and platelet aggregation was reduced by a tea pigment [84]. Studies on monkeys and dogs [85] showed that flavonoids like myricetin, quercetin and kaempferol inhibited the aggregation of platelets. Investigations showed that free radicals are scavenged directly by flavonols and hence this maintains a good concentration of nitric oxide and endothelial prostaglandins [86]. It was reported that flavonoids inhibit the AA pathway by different mechanisms, hence preventing

platelet aggregation indirectly. *Invitro* studies by Van Wauwe *et al*., showed that to the membrane of platelets, flavonoids bind and hence over a time period have an accumulation effect [87].

IV. Flavonoids as anti-gastric ulcer agents

By inhibiting Protein Kinase C (PKC), protein phosphorylation and Cyclooxygenase (COX) formation, flavonoids inhibit gastric ulcer. Investigations also revealed that flavonoids act as favorable substitutes for the usual therapeutic agents. Acylated flavonoids were used as a substitute for aspirin to treat gastric cancer [88]. Gastric acids caused by aspirin were found to decrease in the presence of flavonoids from *Ocimum basilium.* Studies in rats by Tapas *et al*., showed that intraperitoneally administered rutin, quercetin and kaempferol (25-100mg/kg body weight), dose dependently inhibited gastric damage caused by ethanol [89].

V. Flavonoids and Atherosclerosis

Atherosclerotic changes are promoted when the oxidation of Low Density Lipoproteins (LDLs) takes place in the presence of oxygen radicals. This causes damage to the endothelial walls and hence causes atherosclerosis. Literature, showed that regular intake of flavonoids prevented coronary heart disease [90, 91] and death caused by the disease in older men. Aria *et al*., described that the intake of flavonoids and the total plasma cholesterol levels are inversely related [92]. Furthermore, an inverse correlation was found between flavonoid intake and incident dementia [93]. The effects of flavonoids on other cardiovascular diseases are tabulated (Table 3).

Table 3
The effect of flavonoids on cardiovascular diseases

Sl.no	Cardiovascular diseases	Influence of flavonoids	Reference
1.	Arrhythmia	Oxidative stress is decreased	88
2.	Heart Failure	Scavenging of Reactive Oxygen Species	88
3.	Acute myocardial infarction	Inhibition of platelet aggregation	94
4.	Hypertension	Inhibition of NADPH oxidase	94
5.	Atherosclerosis	Decreased in leucocyte adhesion	89

VI. Flavonoids and Osteoporosis

Studies by Hegarty *et al* reported that in elderly women who drank regular tea had increased bone density when compared to those who did not consume tea at all. The researchers proposed that the presence of flavonoids in tea could be the reason for its protective effect against osteoporosis [95].

VII. Flavonoids and Rheumatic Arthritis

Inflammation and autoimmunity are significant components of rheumatic disease. Painful joints are mainly associated with rheumatitis. Orally consumed flavonoids were found to be useful in the destruction of prostaglandins which are responsible for the pain. Flavonoids were also found to activate T-Lymphocytrs that kill cells carrying the antigens and hence prevents inflammation of the joints [95]

VIII. Anti-Allergic Activity of Flavonoids

Calcium-dependent Adenosine Triphosphate (ATPase) and cyclic Adenosine Mono Phosphate (cAMP) phosphodiesterase are important mediators for the release of histamines from basophils and mast cells [5]. Carlo *et al*., revealed that quercetin is a very useful anti-allergic flavonoid useful in conditions like hay fever and asthma. It prevents the immune cells and has a negative influence on the release and production of histamines [96].

IX. Antimicrobial activity of flavonoids

Wang *et al* [97], found that flavonoids had an anti-viral activity. They interfered with viruses such as adenovirus, respiratory syncytial virus, herpes simplex virus and para-influenza virus. Kaul *et al*., described that flavonoids like quercetin interfered with the infective and

replicative abilities of viruses [98]. *Invitro* studies have only been done so far to prove the antiviral effects of flavonoids; still *invivo* studies are needed to describe the mechanisms in detail. Studies on rotaviruses showed that glycone form of the flavonoids were more effective than the aglycone forms [99]. Flavonoids such as anti-HIV compound have been studied nearly for 20 years now. The studies concentrated on the inhibitory action of reverse transcriptase along with the anti-protease and anti-integrase activities of flavonoids. Different flavonoids were also found to have anti-fungal and anti bacterial activities [100] (Table 7).

X. Flavonoids and Diabetes mellitus

Diabetes mellitus is a chronic disease that requires the proper control of the glucose levels in blood (101). Diabetes mellitus is mostly of genetic origin; hence all flavonoids cannot cure the disease. Studies by Havsteen *et al*., have revealed that some flavonoids can control Diabetes mellitus [88] by acting as potential inhibitor of aldose reductase [102]. Many researchers have proved quercetin and chrysin to be a significant anti-diabetic flavonoid that acts by releasing insulin and by regenerating pancreatic islet cells. Studies also revealed that quercetin can stimulate the uptake of calcium ions from the islet cells and thus a potential drug for non-insulin dependent diabetes [89]. Flavonoid fisetin was found to be effective at a concentration of 10 mg/kg body weight to treat Diabetes mellitus [103].

Table 4
Anti-microbial activities of Flavonoids [100]

S.No	Properties	Organism	Flavonoid
1.	Anti-fungal property	*Fusarium solani* *Botrytis cinerea* *Candida tropicalis* *Candida albicans* *Azotobacter vinelandii* *Verticillum dahlia*	Chrysoerol, Quercetin Chlroflavonin, Epicatechin Echinacin, Rutin, Apigenin, Phaseolinisoflavan
2.	Anti-bacterial activity	*Staphylococcus aureus* *Staphylococcus albus* *Streptococcus baris* *Escherichia coli* *Bacillus subtilis* *Proteus vulgaris* *Bacillus anthracis*	Quercetin,Fisetin, Baicalin, Hesperitin,Apigenin, Rutin, Chrysin,Datisetin, Naringin
3.	Antiviral property	*Herpes virus* *Polio virus* *Pseudorabies virus* *Pasrinflenza virus* *Immuno-deficiency virus* *Mengo virus* *Respiratory synctial virus*	Quercetin, Rutin, morin, naringin

XI. Anti-Toxic Activity of Flavonoids

In the liver, flavonoids have the capacity to bind to RNA polymerase I and hence increase protein production. This helps in the formation and regeneration of hepatocytes [5]. Studies revealed that aqueous fenugreek leaf extracts rich in flavonoids ameliorated pesticide induced hepatotoxicity and nephrotoxicity in male wistar rats[104]. Venoruton and rutin were reported to enhance liver regeneration in experimental cirrhosis [89]. Studies by Kim *et al* showed that isolated trifolin, isovitexin, quercetin, hirustin and avicularin had hepatoprotective activity in HepG2 cell lines [105]. Gulati *et al*., investigated and proved quercetin as a potential hepatoprotective agent [106]. In human liver cell lines (Hep 2), different flavonoids such as luteolin, apigenin, quercetin-3-O-glucoside and kaempherol 3-O-glucoside showed hepatoprotective activity [107]. Summary of the effects of flavonoids on various diseases are tabulated in table 8.

Table 5
Summary of the effect of flavonoids on various diseases.

SI.NO	DISEASE	FLAVONOID	MECHANISM	REFERENCE
1.	Inflammation	Quercetin, catechin, rutin, apigenin, fisetin, hesperidin, kaempferol, myricetin, fisetin.	Inducible Nitric Oxide Synthase (iNOS) and COX, PG synthesis	89, 108, 109, 110
2.	Thrombosis	Quercetin, rutin, sinesetin, catechol, hesperidin.	Erythrocyte aggregation, vascular permeability.	111
3.	Ulcer- Peptic and Gastric ulcer	Catechins, quercetin, kaempferol	PG synthesis	89, 111
4.	Atherosclerosis	Quercetin	Decrease in LDL oxidation, inhibition of leucocyte adhesion	88
5.	Osteoporosis	Quercetin	Increase in bone density	95
6.	Rheumatoid arithritis	Rutin, apigenin	Inflammation decreased by acting on COX	112, 108
7.	Anti-allergic	Rutin, quercetin, citrin	Act on mast cells	111, 113, 114
8.	Diabetes mellitus	Quercetin, Fisetin	Inhibits production of aldose reductase	112
9.	Hepatoprotective	Luteolin, quercetin, hirustrin	Binds to RNA polymerse I in the liver	115, 116
10.	Cancer-Lung cancer, oral cancer, tyroid cancer, prostate cancer, colon cancer and breast cancer.	Catechins, luteolin, quercetin, kaempferol, apigenin	Enhance the action of catalase, glutathione reductase, glutathione peroxidase, inhibits the action of tyrosine kinase.	111, 88
11.	Memory dysfunction	Quercetin, fisetin, genistein	Inhibits tyrosine kinase	114

CONCLUSION AND FUTURE IMPLICATIONS

The studies involving flavonoids is complex due to the heterogeneity of various molecular structures. They form a group of biologically active substances that are present in high amounts in plants and consumed in large parts in our daily diet. Flavonoids are gaining more and more importance because of their usefulness and significant roles that they play inside the human body. Future implications involve exploring more potential properties of flavonoids in the field of immunomodulation and anti-toxic activities.

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