Review Article

A Study on Recent Trends in Flavonoids Which Act as Anticancer Agents

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ABSTRACT

The flavonoids are polyphenolic compounds, mainly present in flowering plants, especially in food plants. Humans who consume more vegetables, fruits and green tea, they have very low risk of colon, prostrate and breast cancers. The flavonoid components mediate, the protective effects of diets rich in these food stuffs protects the humans from various types of cancers. The main mechanisms are cell growth inhibition, kinase activity inhibition, apoptosis induction, suppression of the secretion of matrix metallo proteinases, carcinogen inactivation, antiproliferation, inhibition of angiogenesis, antioxidation and reversal of multidrug resistance. These results show that flavonoids may be promising anti-tumor agents.

Keywords: Flavonoids, cancer, flavopiridol, nobiletin, quercetin, myricetin, chrysin.

INTRODUCTION

Cancer is a life threatening metabolic syndrome and is one of the major causes of death. The cancer cells are the potential to spread to other parts of the body. a tumor is said to be malignant it can grow and spread to other parts of the body. There are several types of carcinomas include prostrate cancer, hodkins disease, breast cancer, lung cancer, colorectal cancer, etc. It may spread through the blood stream to distant parts of the body, mainly include the bones, liver, lungs or brain. Flavonoids are polyphenolic molecules containing 15 carbon atoms and are soluble in water. These are the plant secondary metabolite They are in the main classified in to four major teams, like flavanols, flavones, anthocyanidins and isoflavonoids. They are out there as dietary foods and that they cure varied diseases. Flavonoids have the aptitude to control cell division and proliferation. In recent years, flavonoids and their synthetic analogues have been intensely used in the treatment of ovarian, breast, cervical, pancreatic and prostate cancer. The isoflavone analog rotenone is one of the flavonoid compounds, which has been revealed to be actual anticancer agent. Epidemilogical studies shows that long term consumption of diet rich in food and vegetables reduces the risk of cancer [1]

HISTORY

In 1930, rutin a flavonoid obtained from oranges, formerly it is named as vitamin P. Flavonoids mainly found in fruits, vegetables, grains, bark, roots, stems, flowers, tea and wine[2]. There are a variety of factors such as species, variety, climate, degree of ripeness and post harvest storage which influence the concentration of flavonoids in foods[3]. This review mainly focus on the importance of flavonoids as anticancer agents or their therapeutic values as potential drugs.

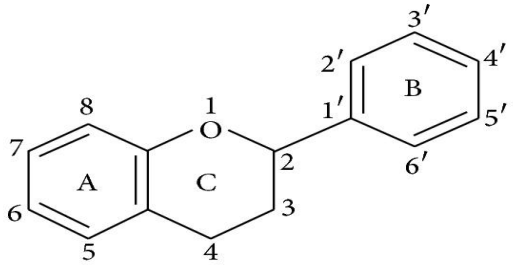

Figure 1: Basic Chemical Structure of Flavonoids

Chemically flavonoids are primarily based upon a fifteen-carbon skeleton consisting of 2 benzene rings (A and B as shown in Figure 1) joined via a heterocyclic pyrane ring (C).

They can be divided into a variety of classes such as flavones (e.g., flavones, apigenin, and luteolin), flavonols (e.g., quercetin, kaempferol, myricetin, and fisetin), flavanones (e.g., flavanone, hesperetin, and naringenin), and others. Their general structures are shown in Table.

The various categories of flavonoids disagree within the level of oxidisation and pattern of substitution of the C ring, whereas individual compounds inside a category disagree within the pattern of substitution of the A and B rings [The three phenolic rings are referred to as the A, B, and C (or pyrane) rings, the flavonoid aglycone consists of a benzene ring (A) condensed with a six membered ring (C) which in the 2-position carries a phenyl ring (B) as a substituent. Six-member ring condensed with the benzene ring is either a pyrone or its dihydro derivative. The position of the benzenoid substituent divides the flavonoid class into flavonoids (2-position) and iso-flavonoids (3-position). Flavonols differ from flavonones by hydroxyl group at 3-position and C2-C3 double bonds.

Flavonoids are typically hydroxylated in position three, 5, 7, 2′, 3′, 4′, 5′. Methyl ethers and acyl group esters of the chemical group are acknowledged to occur in nature.

GENERAL STRUCTURES OF FLAVONOIDS

Flavones

They have a double bond between positions two and three and a ketone compound in position four of the C ring. Most flavones of vegetables and fruits contains a hydroxyl in position five of the a hoop, whereas the hydroxylation in alternative positions, for the foremost half in position 7 of the A ring or 3′ and 4′ of the B ring may vary according to the taxonomic classification of the particular vegetable or fruit. Glycosylation happens totally on position five and seven, methylation and acylation on the hydroxyl groups of the B ring. Some flavones, such as nobiletin and tangeretin, are polymethoxylated.

Flavonols

Compared to flavones, they have a hydroxyl group in position 3 of the C ring, which may also be glycosylated. Again, like flavones, flavonols are very diverse in methylation and hydroxylation patterns as well, and, considering the different glycosylation patterns, they are perhaps the most common and largest subgroup of flavonoids in fruits and vegetables. For example, quercetin is present in many plant foods.

Flavanones

Flavanones, additionally known as dihydroflavones, have the C ring saturated; therefore, unlike flavones, the double bond between positions 2 and 3 is saturated and this is the only structural difference between the two subgroups of flavonoids. The flavanones are often multi-hydroxylated, and several hydroxyl groups can be glycosylated and/or methylated. Some have distinctive patterns of substitution, for example, furanoflavanones, prenylated flavanones, pyranoflavanones or benzylated flavanones, giving a great number of substituted derivatives.

Isoflavones

As anticipated, isoflavones are a subgroup of flavonoids in which the B ring is attached to position 3 of the C ring. They have structural similarities to estrogens, such as estradiol, and for this reason they are also called phytoestrogens.

Neoflavonoids

They have the B ring attached to position 4 of the C ring.

Flavanols or flavan-3-ols or catechins

Flavanols also are said flavan-3-ols because the hydroxyl is sort of invariably guaranteed to position three of C ring; they're known as catechins also. Flavanols to have two chiral centers in the molecule, on positions 2 and 3, then four possible diastereoisomers.

Epicatechin is that the chemical compound with the cis configuration and catechin is that the one with the trans configuration.

Each of these configurations has two stereoisomers, namely, (+)-epicatechin and (-)-epicatechin, (+)-catechin and (-)-catechin.

Anthocyanidins

Chemically, anthocyanidins are flavylium cations and are typically gift as chloride salts. They are the sole cluster of flavonoids that provides plants colours (all alternative flavonoids are colorless). Anthocyanins are glycosides of anthocyanidins. Sugar units are bound mostly to position 3 of the C ring and they are often conjugated with phenolic acids, such as ferulic acid. The color of the anthocyanins depends on the pH scale and additionally by methylation or chemical change at the chemical group teams on the A and B rings.

Chalcones

Chalcones and dihydrochalcones are flavonoids with open structure; they're classified as flavonoids as a result of they need similar artificial pathways.

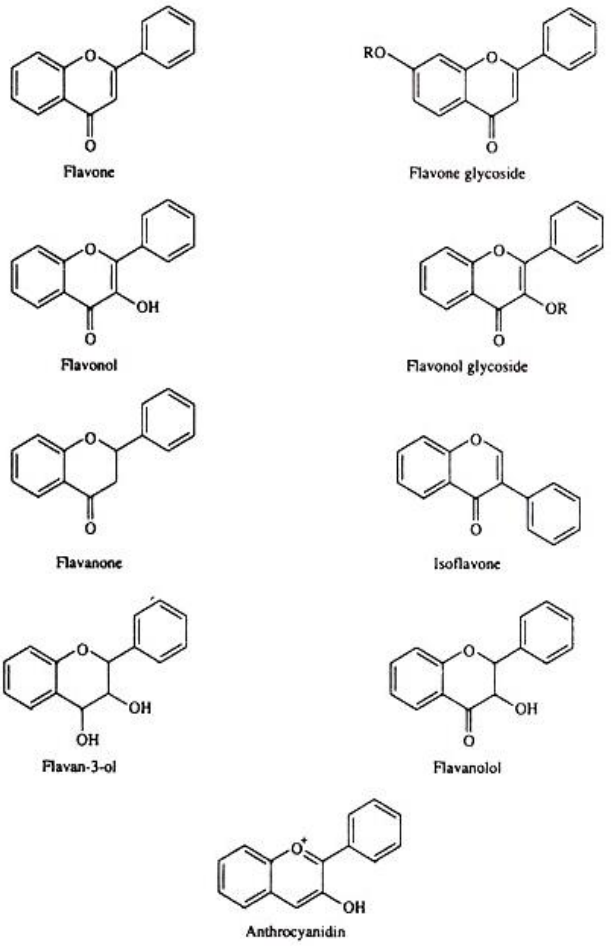

Figure 2: Structure of Some Important Flavonoids

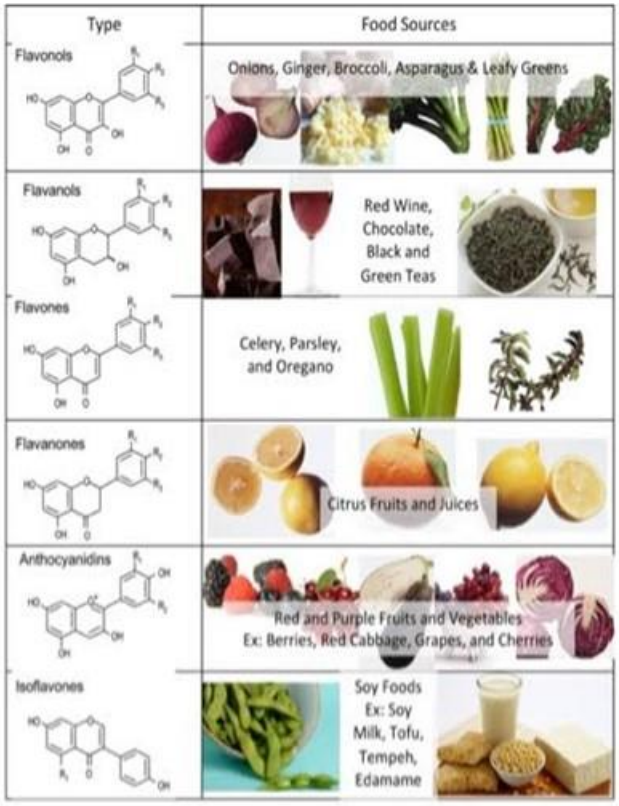

Figure 3: Flavonoid Rich Foods

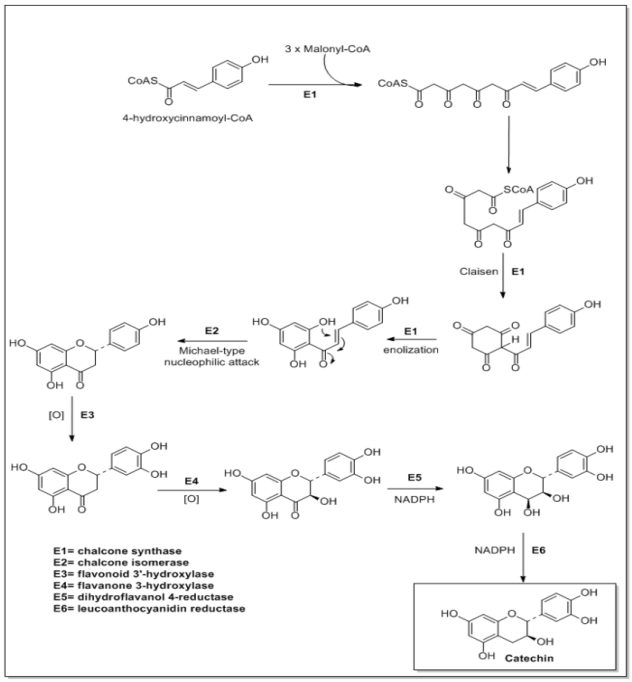

Figure 4: Biosynthesis of Flavonoids

ANTICANCER ACTIVITY OF FLAVONOIDS

• The isoflavone analog rotenone is one of the flavonoid compounds, which have been revealed to be actual anticancer agent. Scutellaria species having flavones retain cytotoxic activities against many human cancer cell lines. At the same time they do not harm the myeloid cells, normal peripheral, normal epithelial blood cells[4].

• Flavone-8-acetic acid (FAA), is an anticancer drug, there are many derivatives of FAA such as xanthenone-4-acetic acid (XAA) and its 5,6 dimethyl derivative (5,6 –MeXAA) that displayed very effective pharmacokinetic properties. 5,6 –MeXAA was 14 fold more potent than the investigational chemotherapeutic drug flavones-8-acetic acid in stimulating tumouricidal activity in cultures of resident murine peritoneal macrophages. 5,6-MeXAA, an another derivative of FAA is a small molecule of flavonoid class that has an antitumor activity due to its ability to induce high local level of tumor necrosis factor that disrupts established blood vessels with in tumors[5]. Another flavonoid silybin and its bioavailable derivative 1Db 1016 enhances the antitumor activity of cisplatin, the most commonly used drug in the treatment of gynecological malignancies[5]

Myricetin-3-o-(L- rhamnopyranoside and quercetin -3-o-lactopyranoside) isolated from *Byrsonima crassa*, *Davilla elliptica*, and mouriri showed antitumor and anti-inflammatory activities[5]

• Trans –bis-(3-amino flavones –kappa 2 N-O) bis copper (11) showed potential antitumor properties[5]

• Flavopiridol, the first CDK inhibitor tested on human, demonstrated clear effects on cell cycle progression, induced differentiation, and apoptosis depending on the relation between transcription factor E2F1 and RB. The drug showed *in vivo* antitumor activity against a variety of tumor xenografts.[6]

• A new flavone glycoside, chrysoeriol 7-0(211 -0-6111 – o –acetyl- beta –D –GLUCOPYRANOSYL – BETA-D – glucopyranoside) showed anticancer activity.[7]

• Nobiletin-a citrus flavonoid from *Citrus depress hayata*, was examined for its antitumor activity on human gastric cancer cell lines. It revealed that it has potent anticancer activity.[8]

• Natural flavones diosmetin showed inhibition of proliferation of breast adenocarcinoma[9]

• Flavonoids rich diets are associated with the reduction of cancer risk in humans. Meditarranean and Asian diets, which are highly rich in flavonoids are often linked to a reduces risk of breast cancer. Increased consumption of isoflavone decreased the risk of estrogen related cancers[9]

• Quercetin 3-o-amino acid –esters, a new type of quercetin derivatives has higher selectivity as inhibitors against SRE tyrosine kinase than EGFR tyrosine kinase[10]

• Luteolin, a flavonoid which suppress the expression of cancer promoting proteins, reduce the tumor size, growth viability and progestin dependent VGF secretion. Luteolin has a significant potential to inhibit proliferation and suppress the breast cancer cells[11]

• Flavonoids are promising anticancer agents compelling data from laboratory studies, epidemiological investigations and human clinical trial indicate that flavonoids have important effect on cancer chemoprevention and chemotherapy[12]

• Dietary agents identified from fruits and vegetables contribute to keeping balanced cell proliferation and preventing cell carcinogenesis.

Dietary flavonoids, combined with other components such as various vitamins, play an important role in cancer prevention.

Flavonoids act on reactive oxygen species, cell signal transduction pathways related to cellular proliferation, apoptosis and angiogenesis[13].

• Flavonoids, mainly flavone-3-ols and proanthocyanins act as potential neutraceuticals; they have the capacity to decrease the risk of cancer by the free radical scavenging properties[14].

• Chrysin (5,7-dihydroxy flavones), has been shown to possess significant antioxidant and anticarcinogenic properties .Chrysin is a hydroxylated flavones chiefly found in honey, propolis and quite a few species of plants for example *Pelargonium crispum, Passiflora incarnate, Oroxylum indicum* etc . Chrysin is able to kill cancer cells of lung, breast, cervical, liver, leukemia, colon, nasopharyngeal, prostrate, giloblastoma, thyroid and pancreatic cancer by promoting apoptosis and moderating cell death by autophagy[15]

• The mechanism of inhibition of polyamine biosynthesis can contribute to the anti-proliferative activities of flavonoids. Ornithine decarboxylase is a rate limiting enzyme in polyamine biosynthesis and is correlated with the rate of DNA synthesis and cell proliferation in several tissues. Several experiments shows that flavonoids will inhibit amino acid enzyme induced by tumour promotes inflicting a sequent dec rease in polyamine and inhibition of polyamine biosynthesis and macromolecule synthesis.[16]Flavones -8 acetic acid (FAA) reduces tumor blood flow dramatically. Several derivatives of FAA were synthesized that showed potent antitumor effect such as xanthenone-4-acetic acid,5,6-MeXAA and FAA have shown potential antitumor activity in several bioreductive drugs by flavopiridol, the first CDK inhibitor tested on human, demonstrated clear effects on cell cycle progression and apoptosis.[16]

CONCLUSION

Flavonoids have the potency to fighting against cancer. They have the potential in modulating many biological processes such as apoptosis, vascularization, cell differentiation, cell proliferation, etc. Some of the dietary flavonoids have shown in vivo antitumor activity. The different types of flavonoids such as diosmetin, Quercetin 3-o-amino acid –esters, Luteolin, Flavones -8 acetic acid, silybin rotenone, Flavopiridol, and Nobiletin shows potential anti cancer activities. So, flavonoids give a new insight for fighting against cancer. Flavonoids have the aptitude to control biological process and proliferation in a vital pathway.

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