Flavonoids: A versatile source of anticancer drugs

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ABSTRACT

An exponential increase in the number of studies investigating how different components of the diet interact at the molecular and cellular level to determine the fate of a cell has been witnessed. In search for anticancer drugs compelling data from laboratories, epidemiologic investigations, and human clinical trials showed that flavonoids have important effects on cancer chemoprevention and chemotherapy. In many molecular mechanisms of action for prevention against cancer, flavonoids play a major role by interacting between different types of genes and enzymes. Many mechanisms of action have been identified, including carcinogen inactivation, antiproliferation, cell cycle arrest, induction of apoptosis, inhibition of angiogenesis, antioxidation, and reversal of multidrug resistance or a combination of these mechanisms. This review focuses on the anticancer activity of flavonoids as well as their molecular mechanisms, including the treatment of mammary and prostate cancer. This review also highlights some advanced derivatives of flavonoids, which play an important role against cancer.

Key words: Apoptosis, estrogens receptor, flavonoids, mammary cancer, prostate cancer

INTRODUCTION

More than 8000 different compounds of polyphenols have been known and that can be further divided into 10 different general classes.[1] Flavonoids are part of this family & have more than 4000 varieties. They have been classified according to their molecular structure that consists of two benzene rings joined by a linear three-carbon chain and forms an oxygenated heterocycle (C6-C3-C6) and their large number arises from the various combinations of multiple hydroxyl, methoxyl, and O-glycoside group substituents on the basic benzo--pyrone (C6-C3-C6)[2] moiety.

Flavonoids are one of the common components in the human diet. They are present in foods generally as O-glycosides with sugars bound at C3 position. Average intake of all flavonoids is estimated to be 1 g/day.[3] Phenolic acids, flavonoids, stilbenes, and lignans are the most abundantly occurring polyphenols in plants out of which flavonoids and phenolic acids account for 60% and 30%, respectively, of dietary polyphenols. Major sources of polyphenols are fruits, vegetables, and seeds. Flavonoids are widely present in the genus Citrus (family Rutaceae).[4]

They exhibit properties beneficial for human health because they interact with number of cellular targets, such as anti-oxidant and free-radical scavenger activities also the anti-inflammatory, antiviral, and especially anti-cancer properties. Cancer chemoprevention by use of natural or synthetic substances and its prevention through dietary intervention has become an important issue. It may be controlled by various means, including suppression, blockage, and transformation. Suppressing agents prevent the formation of new cancers from procarcinogens, blocking agents prevent carcinogenic compounds from reaching critical initiation sites, and transformation agents facilitate the metabolism of carcinogenic components into less toxic materials or prevent their biological actions. Flavonoids can act in all the three ways.[5] Many other potential chemopreventive polyphenols may interrupt or reverse the carcinogenesis process.[6]
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activities. They may therefore have beneficial health effects and can be considered as chemopreventive or therapeutic agents against cancer.

Carcinogenesis is generally considered as a complex and multistep process in which distinct molecular and cellular alterations occur, & to simplify the different possible options for chemoprevention and chemotherapy in cancer development and progression, three stages have been described.

(i) Initiation is a rapid phase, comprises of exposure and interaction of cells, especially DNA, with a carcinogenic agent.
(ii) Promotion is relatively lengthy than the previous stage, abnormal cells persist, replicate and may originate a focus of proneoplastic cells.
(iii) Progression stage is the final phase of the tumorigenesis that involves the gradual conversion of premalignant cells to neoplastic ones with an increase in invasiveness, metastasis potential, and new blood vessel formation (angiogenesis) [Figure 1].

One of the most exciting discoveries is the identification of oncogenes. More than 40 oncogenes have been identified and their protein products have been characterized. These include protein kinases, GTP-binding proteins, and nuclear transcription factors. A unique hypothesis that the activation of transformation might act via protein phosphorylation came into existence. Protein-tyrosine kinases (PTKs) are the group of enzymes that catalyze the transfer of the phosphate of ATP to the hydroxyl group of tyrosine on many key proteins, which in turn induce the cascade of altered cell parameters, a characteristic of transformed cells. This hypothesis has been supported by several recent findings:

1. Activated PTKs have been identified to be the products of approximately half of the known viral transforming genes (oncogenes) [Table 1].
2. The plasma-membrane receptors for several polypeptide growth factors, such as epidermal growth factor (EGF), transforming growth factor-α (TGF-α), platelet-derived growth factor (PDGF), insulin-like growth factor-1 (IGF-I), macrophage colony stimulating factor-1 (CSF-I), fibroblast growth factors (FGF-1 and FGF-2), nerve growth factor (NGF), and hepatocyte growth factor (HGF) are ligand-activated PTKs [Table 1].

Biomolecular activities of flavonoids
- Antioxidative effects: inactivation of oxygen radicals
- Binding of electrophils
- Induction of protective enzymes: phase 2 with conjugating activities (GT, GST)
- Apoptosis rate increase
- Cell proliferation inhibition
- Lipid peroxidation inhibition
- Angiogenesis inhibition
- H-Donation (e.g. GSH-peroxidases)
- DNA oxidation inhibition
- GST, glutathione S-transferases; GT, glucuronosyl transferases; GSH, glutathione.

Figure 1: Three stages of cancer development and progression

The biological properties of citrus flavonoids and the effectiveness of polyphenolics in tea regarding cancer prevention and induction of apoptosis have been widely studied. Flavonoids from Brussels sprouts and flavones induce protective enzymes, such as conjugating enzymes, for example, uridine 5’-diphospho (UDP)-GT, GST in gut and liver. These enzymes inactivate electrophils, free radicals, and reactive oxygen species (ROS) and thereby preventing them from becoming mutagens.

Figure 1 demonstrates the potential mechanisms of inhibition of

<table>
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<th>Table 1: Examples of protein-tyrosine kinase gene families</th>
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<tr>
<td>a. Receptor type genes</td>
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<tr>
<td>1. EGF-R sub-family</td>
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<td>2. I-R sub-family</td>
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<td>3. PDGF-R sub-family</td>
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<td>4. FGF-R sub-family</td>
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<tr>
<td>b. Cytoplasmic type genes</td>
</tr>
<tr>
<td>1. SRC sub-family</td>
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<tr>
<td>2. FES sub-family</td>
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<td>3. ABL sub-family</td>
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carcinogenesis by flavonoids & mainly illustrates the inhibitory effects of tea flavonoids on the main biological events that can lead to mutagens and shows how the carcinogenic neoplastic processes (initiation, promotion, and progression) are influenced.

Preventing carcinogen metabolic activation
One of the most important mechanisms by which flavonoids can exert their effects is through their interaction with phase I metabolizing enzymes (eg, cytochrome P450), which metabolically activate a large number of procarcinogens to reactive intermediates that can interact with cellular nucleophiles and ultimately trigger carcinogenesis. Flavonoids inhibit the activities of certain P450 isozymes, such as CYP1A1 and CYP1A2,[21,22] thus they are likely to have a protective role against the induction of cellular damage by the activation of carcinogens. Another mechanism of action is the induction of phase II metabolizing enzymes (eg, GST, quinone reductase, and UDP-GT)[23,24] by which carcinogens are detoxified & eliminated from the body. This helps in explaining the chemopreventive effects of flavonoids against carcinogenesis [Figure 2].

Antiproliferation
The molecular mechanism of antiproliferation may involve the inhibition of the prooxidant process that causes tumor promotion. Growth promoting oxidants and ROS are the major catalysts of the tumor promotion and progression stages. Flavonoids are effective in inhibiting xanthine oxidase,[25] COX or LOX55,[26] and therefore inhibit tumor cell proliferation.

In addition, the mechanism of inhibition of polyamine biosynthesis can contribute to the antiproliferative activities of flavonoids. Ornithine decarboxylase is a rate-limiting enzyme in polyamine biosynthesis & is correlated with the rate of DNA synthesis and cell proliferation in several tissues. Several experiments show that flavonoids can inhibit ornithine decarboxylase induced by tumor promoters causing a subsequent decrease in polyamine and inhibition of DNA and protein synthesis.[27-29]

Cell cycle arrest
Perturbations in cell cycle progression may account for the

**Figure 2:** Hypothesis of inhibition of carcinogenesis by flavonoids- LOX, Lipooxygenase; COX, Cyclooxygenase; Px, Peroxidase; ROS, Reactive oxygen species; GSH, Glutathione; GST, Glutathione S-transferases; GT, UDP-Glucuronosyl transferases; Px, Peroxidase; NSAID, Nonsteroidal antinflammatory drugs
anticarcinogenic effects of flavonoids. Due to mitogenic signals, cells enter into a series of regulated steps allowing traverse of the cell cycle, and cyclin-dependent kinases (CDKs) are recognized as key regulators of cell cycle progression. Alteration and deregulation of CDK activity are pathogenic hallmarks of neoplasia. Various types of cancers are associated with hyper activation of CDKs due to mutation of CDK genes or CDK inhibitor genes. Therefore, inhibitors or modulators are of great interest as novel therapeutic agents in cancer.[30,31] Checkpoints at both G1/S and G2/M of the cell cycle in cultured cancer cell lines have been found to be perturbed by flavonoids, such as silymarin, genistein, quercetin, daidzein, luteolin, kaempferol, apigenin, and epigallocatechin 3-gallate.[32-34] Studies from various laboratories have revealed that flavopiridol could induce cell cycle arrest during either G1 or G2/M by inhibiting all CDKs.[30,35]

Induction of apoptosis

The significant anticancer properties observed in flavonoids may be due to frank apoptosis.[36-39] Apoptosis is an active form of cell death that plays an essential role in the development and survival by eliminating damaged or unwanted cells. It is tightly regulated by a set of genes that promote apoptosis cell survival and is mediated through a highly organized network of interacting protease and their inhibitors in response to noxious stimuli from either inside or outside of the cell. Dysregulation of apoptosis plays a critical role in oncogenesis. Flavonoids have shown to induce apoptosis in some cancer cell lines, while sparing normal cells. The molecular mechanisms by which flavonoids induce apoptosis have not been clarified. Several mechanisms may be involved, including inhibition of DNA topoisomerase I/II activity,[40-42] decrease of ROS,[43] regulation of heat shock protein expression,[44] modulation of signaling pathways,[45] downregulation of nuclear transcription factor kappa B (NF-κB), activation of endonuclease, and suppression of McI-1 protein.[39,46,47,48]

In vitro studies of flavonoids

In vitro, flavonoids modify the activity of enzymatic systems in mammals (eg, kinases, phospholipases, ATPase, lipoxygenases, cyclooxygenases, and phosphodiesterases). A correlation has been observed in some cases between the flavonoid structure and its enzymatic activity.[47-50] Much of these effects can be attributed to the abilities of flavonoids to interact with the nucleotide binding sites of regulatory enzymes.

Many researchers have conducted in vitro studies on the potential anticancer activity of flavonoids in diverse cell systems. The report on the inhibitory properties of flavonoids against carcinogenesis are summarized in Table 2. Hirano and co-workers examined anticancer efficacy of 28 flavonoids on human acute myeloid leukemia cell line HL-60 and differences between antiproliferative activity and cytotoxicity of these compounds with those of four clinical anticancer agents. Out of 28 flavonoids, 8 showed considerable suppressive effects on HL-60 cell growth with IC$_{50}$s ranging from 10-940 ng/mL. Among these compounds, genistein, honokiol, machilin A, matairesinol, and arctigenin had the strongest effects with IC$_{50}$s less than 100 ng/mL, which were almost equivalent to the effects of current anticancer agents. The flavonoid genistein and the lignans, however, showed little or no cytotoxicity against HL-60 cells as assessed by dye exclusion tests (IC$_{50}$s > 2,900ng/ml), whereas the regular anti-cancer agents had potent cytotoxicity.[47,48] and more than 30 flavonoids were screened for their effects on cell proliferation and potential cytotoxicity in human colon cancer cell lines Caco-2 and HT-29. There was no obvious structure activity relationship in the antiproliferative effects either on the basis of sub-classes with respect to type or position of substituents within a class.[53]

Flavonoids showed inhibition of carcinogenesis in vitro but substantial evidences indicate that they can also do so in vivo.[52,78] Studies on animals and investigations using different cellular models suggest that certain flavonoids could inhibit tumor initiation as well as tumor progression.[57,61,74] Siess and co-workers investigated the effects of feeding rats with flavone, flavanone, tangeretin, and quercterin on two steps of aflatoxin B1 (AFB1)-induced hepatocarcinogenesis (initiation and promotion) and found that flavone, flavanone, and tangeretin administered through the initiation period, decreased the number of γ-glutamyl

| Table 2: Anticancer activities of flavonoids in various cancer cell lines |
|-----------------------------|-----------------------------|-----------------------------|
| Cancer                      | Cell                        | Flavonoid                   | Ref.         |
| Human oral cancer           | HSC-2, HSG, SCC-25          | Flavanones, isoflavones, EGC, chalcones, EGCG, curcumin, genistein, ECG, querctin, cisplatin | [54-57] |
| Human breast cancer         | MCF-7                       | Flavanones, daidzein, genistein, querctin, luteolin                              | [58,59]  |
| Human thyroid cancer        | ARO,NPA, WRO                | Genistein, apigenin, kaempferol, chrys-in, luteolin, biochanin A                  | [38,60]  |
| Human lung cancer           | SK-LU1, SW900, H441, H661, haGo-K-1, A549 | Flavone, quercterin                                                  | [61,62] |
| Human prostate cancer       | LNCaP, PC3, DU145           | Catechin, epicatechin, querctin, kaempferol, luteolin, genistein, apigenin, myricetin, silymarin | [63-66] |
| Human colon cancer          | Caco-2, HT-29, IEC-6, HCT-15 | Flavone, querctin, genistein, anthocyanin                                       | [46, 67-69] |
| Human leukemia              | HL-60, K562, 4A5, B16 mouse melanoma | Jurkat Apigenin, querctin, myricetin, chalcones                                 | [50, 70, 71, 53] [54] |
transpeptidase-preneoplastic foci. Therefore flavanone acts as an anti-initiator as well as an anti-promoter.[73] Lung tumorigenesis is prevented by catechin enriched tea and is demonstrated in A/J mice.[74] Two weeks before the 4-(methylnitrosamine)-1-(3-pyridyl)-1 butanone (NNK) treatment, decaffeinated green or black tea is given to mice for 3 or 15 weeks. This markedly reduced the number of tumors formed in the mice. In those mice adenomas have developed at 16 weeks after the NNK injection; and, the progression of adenomas to adenocarcinomas was significantly inhibited by administration of black tea. These experiments infer that tea has broad inhibitory activity against lung carcinogenesis and it is effective when administered during the initiation, promotion, or progression stages of carcinogenesis. Moreover, there is evidence for the suppression of tumor invasion and metastasis by flavonoids.

Catechins, a group of flavonoid molecules, in vitro[77] inhibit the invasion of mouse MO4 cells into embryonic chick heart fragments. A polymethoxy flavonoid, nobiletin from Citrus depressa inhibits the tumor invasion activity of human fibrosarcoma HT-108 cells in the Matrigel model, by the suppression of expression of matrix metalloproteases (MMPs) and augmenting of tissue inhibitors of metalloproteinases.[78] Quercetin and apigenin inhibited melanoma cell (B16-BL6) growth and metastatic potential in syngeneic mice, in vitro.[80] They were found to significantly decrease the invasion of B16-BL6 cells. Also apigenin significantly decreased the invasion of lymphatic vessel of intestinal adenocarcinomas that are induced by azoxymethane and are of cancer peritoneal metastasis, enhanced by bombesin in male Wistar rats. The inhibitory effect of apigenin on cancer metastasis may be through the inhibition of phosphorylation of mitogen-activated protein kinase (MAPK).[79]

TREATMENT OF DIFFERENT TYPES OF CANCER BY FLAVONOIDS

In Western countries, breast cancer is one of the most common causes of death in women and prostate cancer is the second most common cause of death in men. In China, Japan, and other Asian countries, where diets include relatively high concentrations of soy isoflavones, death due to cancer is comparatively rare.[80]

Phytoestrogens are plant-derived chemicals that bind to the estrogen receptor (ER) and induce various estrogenic and antiestrogenic responses.[81] The extensively studied class of phytoestrogens are the isoflavones. High concentrations of the isoflavones genistein and daidzein are present in legumes and ingestion of these substances may reduce the risk of cancer, particularly in the breast and prostate.

Experimentally, thoroughly studied soy isoflavone is genistein. It is clear, however, that in vitro micromolar concentrations of genistein can inhibit the growth of a wide variety of cancer cells. [81] In ER-positive cells, growth inhibitors compete with estradiol for receptor binding, and translocation of the hormone-receptor complex takes place in the nucleus and ultimately, reduce the stimulation of a variety of downstream effects.[82]

Soy containing isoflavones are among the most versatile biopharmaceuticals known. Genistein, daidzein, and glycitein are the main isoflavones found in soy foods [Figure 3]. Isoflavones, one of the major class of phytoestrogens, are structurally similar to estrogens,[83] binds to ERs, and hence have estrogenic and anti-estrogenic activities and their own growth-inhibitory effects are independent of ER.[84,85] Isoflavones and their metabolites are considered to reduce the risk of cancer and to have potent anticarcinogenic activities[86,87] by direct inhibition of PTK,[88] inhibition of DNA-topoisomerase II,[89] inhibition of angiogenesis,[90] antiproliferation, and cell cycle arrest,[90] and induction of apoptosis.[91]

Two major types of cancer and their treatment using flavonoids are discussed in the following sections.

MAMMARY TUMOR

Evidences support that estrogens are involved in mammary carcinomas. Researchers have found that in ER-positive and ER-negative mammary cell lines of women affected with breast cancer, the tumor-suppressing gene pRb2/p13 binds to a specific region on the ER gene alpha and forms molecular complexes recruiting and interacting with several proteins. They discovered that ER-negative cells that are able to silent the expression of the ER pRb2/p13 form a specific molecular complex recruiting a different sequence of proteins than in the ER-positive cells. Our hypothesis is that the sequence of epigenetic events for establishing and maintaining a silence state of ER gene alpha during the breast cancer progression is mediated by pRb2/p13 in association with specific proteins that modify the DNA structure through specific mechanisms.[92]

 Estradiol, the most potent endogenous estrogen, is biosynthesized from androgens by cytochrome P450 enzyme complex called aromatase. Some flavonoids have been reported as potent aromatase inhibitors.[93-95] Therefore, flavonoids are considered as potential agents against breast cancer by inhibiting aromatase activity.

Investigation of seven metabolites of isoflavones for their growth-inhibitory effects and later compared with the isoflavones genistein, daidzein, and glycitein present on human breast cancer MCF-7 and MDA-MB-468 cells. The novel metabolite 2-de-O-DMA exhibited a potent growth inhibitory effect on human breast ER-positive MCF-7 cells and ER-negative MDA-MB-468 cells. This metabolite was further examined on other human breast cancer SK-BR-3 (ER-negative), human breast noncancer MCF-10A (ER-negative), human prostate cancer LNCaP [androgen receptor (AR)-positive], and DU145 (AR-negative) cell lines. Hence this study shows that the novel metabolite 2-de-O-DMA is still able to inhibit the proliferation...
Epidemiologic studies have showed that populations with high isoflavone intake through soy consumption have low rates of breast, prostate, and colon cancer. The isoflavone polyphenol genistein in soybean is considered to be a potent chemopreventive agent against cancer.

**PROSTATE CANCER**

Prostate cancer (PCA) is considered as one of the major concerns in the field of cancer therapy. PCA is an aging disease and oxidative stress is a major factor in the promotion/progression of malignancy. Furthermore, activation of many kinases involved in NF-κB pathway is dependent on oxidative stress. ROS cause prolonged NF-κB DNA binding activity and antioxidants have shown to diminish this activity. Based on the above study, one approach to control PCA growth and progression can be inhibition of constitutive NF-κB activation, however, limited efforts have been made in this direction. Some flavonoids play an important role in preventing PCA by various modes of action.

Silibinin is a flavonolignan present in milk thistle seeds. It is a promising chemopreventive agent against human PCA without showing any apparent toxic side effects. Silibinin has shown strong anticancer efficacy against both androgen-dependent and -independent advanced human PCA cells. Silibinin inhibits TGF expression, secretion, and down-regulates EGFR-Erk1/2 activation in both LNCaP and DU145 cells, which contributes to the growth inhibitory effects in these cell lines.

Recently, at pharmacologically achievable silibinin concentrations (0.02-20 µM) observed increased insulin-like growth factor-binding protein 3 (IGFBP-3) accumulation in PC-3 cell conditioned medium and a dose-dependent increase of IGFBP-3 mRNA abundance with a 9-fold increase over baseline at 20 µM silibinin. Silibinin also showed, effect on membrane signaling related to erbB1 activation in human PCA LNCaP and DU145 cells. Activation of NF-κB by cytokines is mediated by signal transduction cascades, leading to activation of the IκB kinases, IKKα and IKKβ. Silibinin inhibited the constitutive activation of NF-κB and IKKα in PC-3 and DU-145 cells, and blocked stimulated activation of NF-κB in LNCaP cells. Lastly, the results clearly indicate that silibinin effectively sensitizes DU145 cells to cisplatin- and carboplatin-induced growth inhibition and apoptosis, possibly via an increase in G2M arrest suggesting that studies done in vivo are needed in pre-clinical PCA models of such combinations, which might provide scientific base in

**Figure 3:** Some of the isoflavones found in soy foods
developing more effective treatment against human PCA.

Luteolin (30,40,5,7-tetrahydroxyflavone) has an antiproliferation property that acts via arresting cell cycle and apoptosis in many human cancer cells, including PCA cells.[107,108] Studies showed that luteolin inhibits the expression of AR and growth in LNCaP human PCA cells and xenografted mice. The reduction in AR levels by luteolin involve a transcriptional or post translational mechanism. Moreover, it suggests that luteolin suppresses the association between AR and heat-shock protein 9 (Hsp90) and induces AR protein degradation through a proteasome-mediated pathway.[109] These results indicate that AR is critical for PCA cell growth and survival and that it is a potential molecular target for luteolin-mediated anticancer therapy.

Quercetin exerts the strongest expression of MMP-2 and -9 through the inhibition of protein kinases. Quercetin inhibits the secretion of MMP-2 also in tumor cells and thereby reduces the potential for metastasis.[110-112] Quercetin also acts as a preventive agent against cancer invasion. By targeting specific genes that regulate the expression of MMPs can be advantageous in the treatment of PCA.

Nutritional science contributes substantially also. Identification of biomarkers plays an important role in this effort through the use of new and emerging technologies. At the same time, gene expression profiling and proteomics provide novel insights into cancer-related traits. Early detection is the desired strategy for reducing cancer-related morbidity and mortality, and collaborative effort between academic and industry leaders brings expert solutions for cancer.

**ADVANCED DEVELOPMENT OF ANTICANCER AGENT FROM NATURAL FLAVONOIDS**

In the search for anticancer drugs from botanical sources, plant extracts were fractionated by various means and were then *in vitro* tested for anticancer properties. Here, we discuss flavonoid compounds that display their anticancer activity in recent time, including those that are able to influence processes that are dysregulated during cancer development.

(a) Flavone 8-acetic acid (FAA) represents a novel chemical structure undergoing clinical trials as an anticancer drug. Most unusual property of FAA is its ability to reduce tumour blood flow dramatically, which may provide the appropriate conditions for reactive chemistry to occur which distinguish it from a conventional cytotoxic compound, particularly in the response of solid murine tumors.[113] Its clinical use has a number of pharmacologic drawbacks, including low dose potency and dose-dependent pharmacokinetics. So in search for better analogs of FAA-, several derivatives of FAA were synthesized that showed potent antitumor effect, such as xantheneone-4-acetic acid (XAA) and its 5,6-dimethyl derivative (5,6-MeXAA) that displayed very effective pharmacokinetic properties.[114,115] 5,6-MeXAA (NSC 640488) was 14-fold more potent than the investigational chemotherapeutic drug flavone-8-acetic acid (NSC 347512) in stimulating tumouricidal activity in cultures of resident murine peritoneal macrophages.[116] 5,6-MeXAA, another derivative of FAA is a small molecule of flavonoid class that has an antitumor activity due to its ability to induce high local levels of tumor necrosis factor (TNF) that disrupts established blood vessels within tumors.[117,118] 5,6-MeXAA and FAA have shown potential antitumour activity in several bioreductive drugs by inhibiting enzyme DT-diaphorase (NAD(P)-H Quinone oxidoreductase EC 1.6.99.2) with respect to NADH, Ki values of 75 and 20 µM, respectively.[118,119] Also fluorene derivative of FAA bearing a fluorene atom at the 7th position is a most active compound showing remarkable activities in murine cells, but not confirmed in human models.[119]

(b) 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.[121,122] Flavopiridol undergoes Phase II single-agent trials and Phase I combination trials (with paclitaxel and cisplatin). The drug showed *in vivo* antitumor activity against a variety of tumor xenografts.[123,124]

(c) A new flavone glycoside, chrysoeriol 7-O-((2''-O-6'''-O-acetyl-β-D-glucopyranosyl)-β-D-glucopyranoside (1), along with 14 known compounds (2-15) was isolated from *Cardus crispus* Linn. plant. The antitumor activity of compound (1), (4) and (5) was also tested.[125]

(d) Nobiletin (5,6,7,8,3''-4''-hexamethoxyflavone)-, a citrus flavonoid-, extracted from *Citrus depressa* Hayata, was examined for its antitumor activity on human gastric cancer cell lines. Cell-cycle analysis revealed that nobiletin acted on these cells through several ways, namely, by direct cytotoxicity, induction of apoptosis, and modulation of cell cycle.[126]

(e) The flavonoid silybin and its bioavailable derivative IdB 1016 (silipide) enhance the antitumor activity of cisplatin (CDDP), the most commonly used drug in the treatment of gynecologic malignancies [Figure 4].[127]

(f) Natural flavone diosmetin showed inhibition of proliferation of breast adenocarcinoma MDA-MB 468 and normal breast MCF-10A cells and was found that this compound is selective for the cancer cells with slight toxicity in the normal breast cells.[128]

(g) Quercetin 3-O-aminoc acid-esters, a new type of quercetin derivatives have been successfully prepared for the first time. Different from quercetin, the novel compounds show higher selectivity as inhibitors against Src tyrosine kinase (IC₅₀) than against EGFR tyrosine kinase.[129]

(h) The modified derivative of flavone, such as trans-bis-(3-aminoflavone-kappa2 N,-O)bis (perchlorato kappa O) copper(II), showed potential antitumor properties.[130]

(i) Myricetin-3-O-(L-rhamnopyranoside and quercetin-3-O-lactopyranoside isolated from *Byronima crassa*, *Davilla elliptica*, *
Figure 4: Chemical structure of advanced anticancerous flavonoids
and Mouriri showed antitumor and anti-inflammatory activities.[33]

In the past, many attempts have been made to obtain anticancerous plant originated flavonoids and the efforts will further be continued until a satisfactory treatment becomes available. In this regard, a number of medicinal plants having anticonvulsant potential are reviewed.

REFERENCES


Yin F, Giuliano AE, Van Herle AJ. Growth inhibitory effects of flavonoids in human thyroid cancer cell lines. Thyroid 1999;9:369-76.


111. Vayali PK, Mittal A, Katiyar SK. Proanthocyanidins from grape seeds inhibit Expression of matrix metalloproteinases in human prostate carcinoma cells, which is associated with the inhibition of activation of MAPK and NF kappa B. Carcinogenesis
Activation of Tumor-Associated Macrophages by the Anti-tumour effects of nobiletin, a citrus flavonoid, on isolated flavonoids against mammary Silybin and its bioavailable phospholipid


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