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Flavonoids: Anticancer Properties

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Additional information is available at the end of the chapter

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Abstract

Flavonoids are plant secondary metabolites. They are mainly classified into four major groups, such as flavanols, flavones, anthocyanidins, and isoflavonoids. Furthermore, they are divided into some subclasses. They are available in dietary foods and they cure various diseases. Certain plants and spices contain flavonoids, which have been commonly used for thousands of years in traditional medicine. Some of the flavonoids have been clinically used in many countries. Baicalein and its glycosides are one among them to have been experimented clinically. Flavonoids have the capability to regulate cell division and proliferation in an important pathway. They have medicinal activities including anticancer properties. The isoflavone analog rotenone is one of the flavonoid compounds, which has 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 and normal epithelial blood cells. Epidemiological studies also confirmed that the intake of dietary flavonoids reduces a risk condition in cancer.

Keywords: flavonoids, cancer, dietary foods, pathway, epidemiological study

1. Introduction

Flavonoids are plant-based secondary metabolites. The intake of flavonoids is always safe and without adverse effects. Recent studies also suggest that the consumption of different fruits and vegetables has the capability to fight against cancers and decrease the cancer risk level at least by 20%. Based on this, the scientific community has focused its attention on plant-based compounds in order to control cancers. Many compounds, such as flavonoids, were isolated from plants and shown to have anticancer activity notably. This was confirmed through *in vitro* and *in vivo* studies [1]. Our dietary foods contain different types of flavonoids

in various food additives. Grains and herbs have flavones. Fruits and vegetables hold flavonols and their glycosides. Citrus juices, legumes, and tea contain flavanones, isoflavones, and catechins, respectively. Some flavonoids are able to fight against breast cancer [2]. The health benefits of flavonoids may be helpful to find new drug discoveries. Such compounds are listed with their specific subclasses. Apigenin, baicalein, luteolin, and chrysin belong to the subclass of flavones; kaempferol, myricetin, and quercetin are closer to the subclass of flavonols; hesperetin is flavanone compound; genistein and daidzein go with the subclass of isoflavones; baicalin, catechin, and rutin fit with flavone glycosides, flavan-3-ols, and flavonol glycosides, respectively. There are different types of tumors which can be organized and categorized as oral (pharyngeal, laryngeal), gastrointestinal (esophageal, gastric, pancreatic), colorectal, liver, reproductive (ovarian, endometrial, prostate), breast, and lung cancer. The various diseases including cancers are controlled by the intake of flavonoids. Cytotoxicity in cancer cell line is shown mainly because of flavonoid compounds which do not affect normal cells. This was proved by cytotoxicity assay. Apigenin and luteolin come under the flavonoid subclass, flavones which have the ability to regulate macrophage function in cancer cell elimination and act as a potential inhibitor of cell proliferation. Many *in vitro* and *in vivo* studies confirmed that flavonoids have good activity against various cancer cell lines. Flavonoids have the ability to perform antiproliferation and cytotoxicity in cancer cell lines. They are used for human clinical trial which was conducted on flavone acetic acid.

In 2011, a database of U.S Department of Agriculture explains to us the flavonoid content in 500 foods in which isoflavone, proanthocyanidin, and other compounds are identified [3]. This definitely helps us calculate the flavonoid intake and its cancer-preventive properties. The amount of intake and the time of exposure have considerable say in the anticancer response to flavonoid-rich diets. Some intervention trials of flavonoids have shown their capacity to prevent cancer. They have the ability to block cell cycle followed by apoptosis. In recent years, they have been used for the treatment of prostate, pancreatic, breast, cervical, and ovarian cancers. Several protein kinases, epidermal growth factor receptors (EGFRs), platelet-derived growth factor receptors (PDGFRs), vascular endothelial growth factor receptors (VEGFRs), and cyclin-dependent kinases (CDKs) [4] play important roles in cancer pathology. COX (cyclooxygenase), LOX (lipoxygenase), and xanthine oxidase enzymes are also responsible for cancer pathologies. Flavonoids have the power to decrease and sometimes control all these pathogenic factors completely.

2. Anticancer properties of flavonoids

Major classes of flavonoids possess anticancer properties. The sources of flavonoids are also explained in this context. Flavanols are present in strawberries, apple, chocolate, cocoa, beans, cherry, green, and black tea. They have the potential to fight against human oral, rectal, and prostate cancer. The major sources of anthocyanidins are blueberries, blackberries, blackcurrant, and aubergine. These natural resources are used to treat colorectal cancer. The major sources of flavones are Siberian larch tree, onion, milk thistle, acai palm, lemon juice, orange juice, grape juice, kale, cherries, leek, Brussel sprouts, pepper, broccoli, capsicum, parsley,

and celery. They have the ability to fight against breast cancer, lung cancer, leukemia, thyroid, stomach, laryngeal, colon, and oral cancer. Sources of isoflavonoids are soybeans, soy flour, soy milk, beer, and tempeh. They fight against prostate cancer, breast cancer, colon, kidney, and thyroid cancer [5].

2.1. Different groups of flavonoids

Flavonoids are mainly classified into four major groups: flavanols, flavones, anthocyanidins, and isoflavonoids. The major groups of these flavonoids are displayed in the subsequent text (**Figure 1**). A chemical structure of compound is drawn for each flavonoid group (**Figure 2**). Compounds from various subclasses of flavonoids are put together in their respective flavonoid groups. The major classification of flavones and anthocyanidins is displayed in **Figure 3**. Furthermore, they are divided into some subclasses. Among these subclasses, flavan-3-ols contain catechin, gallic catechin, catechin-3-gallate, epicatechin, and epigallocatechin (EGC). Kaempferol, myricetin, quercetin, and rutin belong to the subclass of flavonol [5]. Some other compounds are also classified under the specific subclasses of flavonoids (**Figure 3**).

2.2. Epidemiological information for flavonoids

Many studies on the distribution of diseases prove that flavonoids have positive effects in curbing cancer. It has been evidenced by various studies that the possibility of developing cancer could be reduced if more amount of flavonoid is administered [6, 7].

There was a case-control type study on 250 breast cancer-positive individuals based on population in Shanghai from 1996 to 1998. It was revealed in the corresponding controls; Dai et al. [8] noted that the number of breast cancer-positive individuals had less of isoflavonoids as well as lignans compared to the controls (urine sample of the cancer-positive individual was taken prior to administering therapy). The middle discharge rate of aggregate isoflavonoids

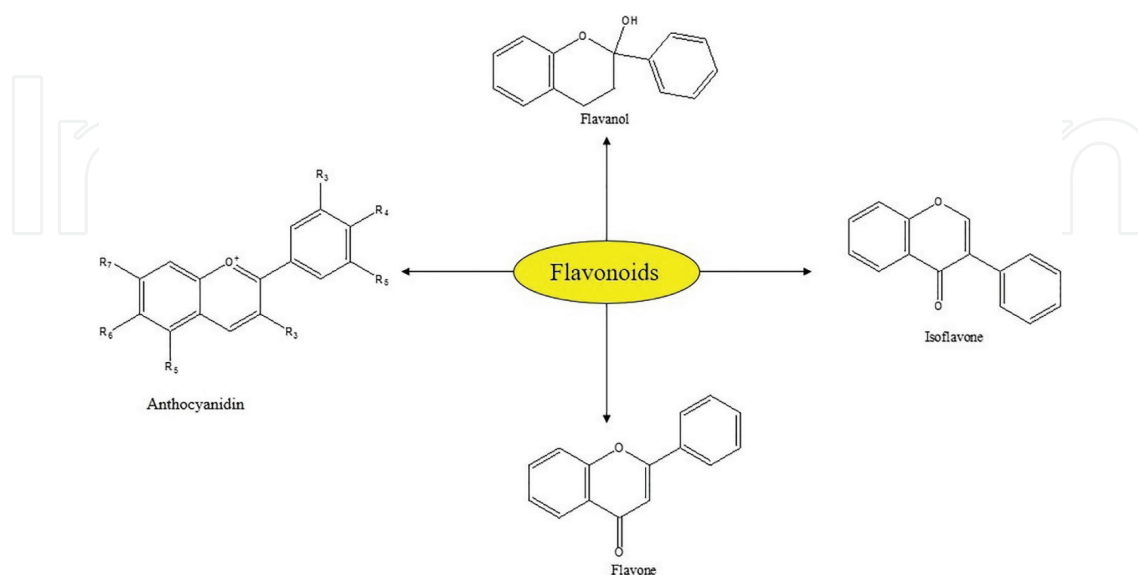


Figure 1. Major classification of flavonoids.

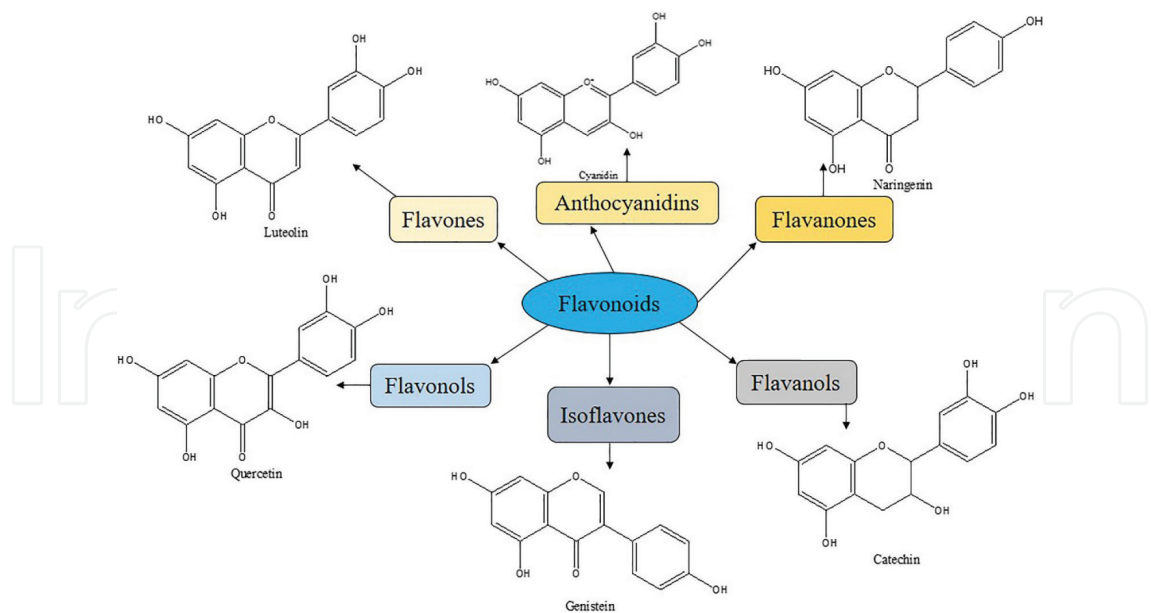


Figure 2. Different classes of flavonoids and their compound chemical structures.

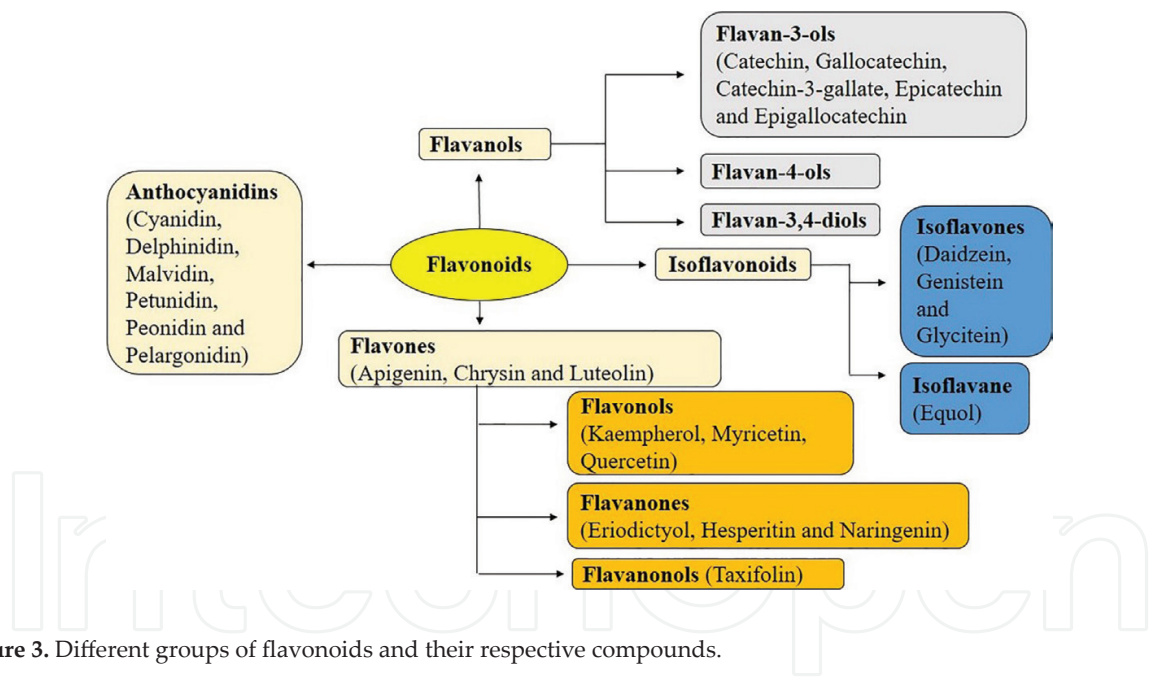


Figure 3. Different groups of flavonoids and their respective compounds.

was 13.97 nmol/mg creatinine in cases and 23.09 in controls ($P = 0.01$), and that of aggregate lignans was 1.77 in cases and 4.16 in controls ($P < 0.01$). Thus, it was recommended that flavonoids are capable of averting breast cancer.

Another lung cancer study was done on the observation of individuals beyond the age of 25. A total number of 9959 lung cancer-positive Finnish men and women between the ages of 25–99 showed reduced lung cancer after administering flavonoids through diet. The inference was made based on vitamin E, vitamin C, beta-carotene, or total calories consumption. There was a study on 10,054 individuals of both men and women by Knekt and coworkers [9] on the amount of flavonoid consumption in Finnish diet. The study revealed a lesser possibility

for lung cancer with the higher consumption of quercetin and the lesser possibility of prostate cancer with more consumption of myricetin. Thus, flavonoids were proved to play a vital role in preventing cancer occurrence.

There was also a case-control work done based on population in Hawaii in order to study in detail the relation between the probability of lung cancer and the consumption of flavonoids through diet. For the study, they took 582 individuals who were lung cancer-positive and the same number of controls of matching age, sex, and ethnicity. The consumption of flavonoids such as onion, white grapefruits, apples, and quercetin was reversely related to the probability of suffering lung cancer [10]. The outcome of the above study is found to be similar to the previous study done in Uruguay on 541 lung cancer-positive individuals and 540 controls but fewer incidents of lung cancer due to vitamin E and beta-carotene.

Besides, it was also found in a case-control work carried out by the group of researchers in Uruguay between 1996 January and 1997 December that reduced incidents of an esophagus, oral cavity, larynx, and pharynx cancer by 70% achieved by flavonoids. Flavonoids like kaempferol and quercetin are also found to be preventing gastric cancer unlike carotenoids like alpha-carotene, lutein, beta-carotene, and lycopene in yet another case-control study carried out in Spain which consisted of 354 gastric cancer-positive individuals and 354 controls. An observation was done on 34,651 women free from postmenopausal cancer between the ages of 55 and 69 during 1986 and 1998. In modification with prospective confounders, the consumption of catechin was reversely related to only the rectal cancer occurrence [11]. These prove the potential ability of flavonoids for a cancer cure.

In this way, the administering of flavonoids is effective in preventing cancer in most if not in all studies. Reports [12] also show that flavonoids are ineffective. It is mainly because of the uneven availability of the same. However, it should not be fully neglected without detailed study.

2.3. Case-control study in cancer

Two case-control studies were conducted in six counties in New Jersey (205 cases of ovarian cancer and 390 controls) [13] and in the North-East United States (1231 cases and 1244 controls). These revealed that there was no link between total flavonoid consumption and ovarian cancer [14]. Some of the cancer case studies have been discussed in the subsequent text.

2.3.1. Gastrointestinal cancers

A case study showed that there is an inverse association between flavanone intake and esophageal cancer, and this could reduce by the intake of citrus fruits. An increased risk of gastric cancer is found among smoking men. The intake of epigallocatechin (EGC) plays an important role to slow down the disease.

2.3.2. Pancreatic cancer

Researchers analyzed the intake of flavonoids and the risk of pancreatic cancer during the study. The results reported that flavonoid-rich diets can decline pancreatic cancer risk in male smokers. Inverse relationships were also found among current smokers between a risk of pancreatic cancer and the intake of total flavonols, quercetin, kaempferol, and myricetin.

2.3.3. Colorectal cancer

Isoflavone intake was inversely related to colorectal cancer risk in men and postmenopausal women. Cases were analyzed in Japan, Netherlands, and in the UK in both men and women regarding the intake of isoflavone and its inverse effect on colorectal cancer. Total catechin, (β)-catechin, myricetin and (-)-epicatechin and kaempferol were effective against colorectal cancer. These results may have associations for the use of dietary flavonoids in the prevention of rectal cancer.

2.4. Inhibition of pro-oxidant enzymes

NADPH oxidase I (NOX 1) enzyme produces superoxide, which is overexpressed in colon and prostate cancer cell lines [15]. Superoxide is one of the reactive oxygen species (ROS). Superoxide dismutase (SOD) is one of the antioxidants which can inhibit a pro-oxidant enzyme (Figure 4). Generally, flavonoids have the ability to inhibit DNA damaging, mutagenic signaling, cell proliferation, and proto-oncogenes (cFOS, cJUN, and cMyc). Diagrams are drawn using Microsoft PowerPoint 2013 and converted to JPEG format.

2.5. Flavonoids from *Scutellaria* species

Wogonin and baicalein from *Scutellaria* species have been tested in a mouse for anticancer activity. *S. baicalensis* has an O-methylated flavone called wogonin and a flavone called baicalein, which were isolated from the roots of the same plant as well as from *S. lateriflora*. A flavone glycoside called baicalin is also found in *Scutellaria* species. Oral administering of 20 mg/kg baicalein was able to inhibit prostate cancer nearly 55%. Both the compounds have therapeutic potential against cancer. The identified flavonoids from *Scutellaria* species are about 60. The reported minor flavonoids from the same species are Apigenin, Luteolin [16], and Chrysin. They possess antitumor activities. *Scutellaria* alone or in combination with other herbs has the cytostatic effect on several cancer cell lines in vitro and in vivo mouse model [17]. One of the anticancer drugs is wogonin. It comes under flavonoids. It is considered as chemotherapeutic agent to decrease their side effects. It has a hepatoprotective effect

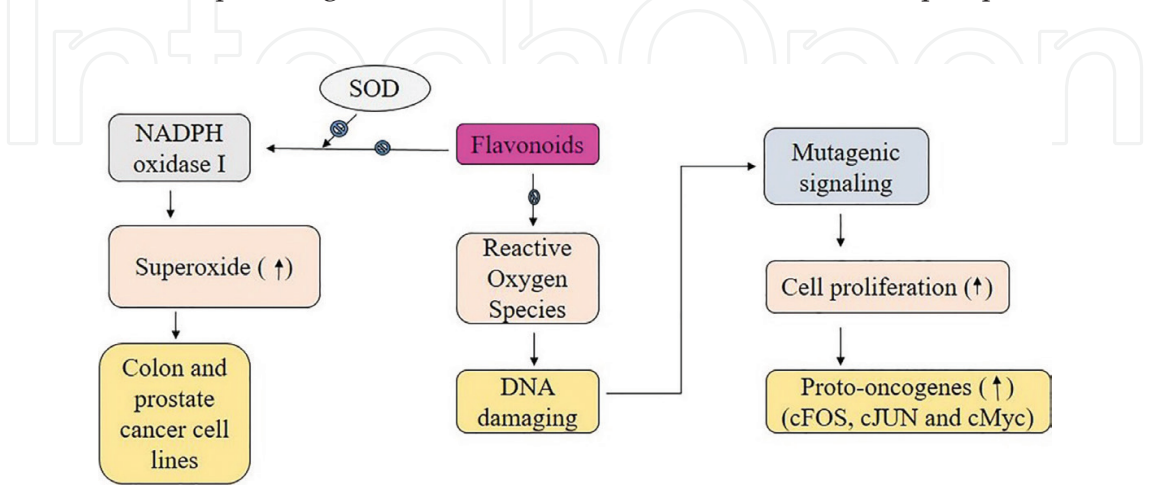


Figure 4. Inhibition of pro-oxidant enzymes.

and prompts apoptosis in caspase 3 pathway. It alternates p21 protein expression. Wogonin and its derivatives possess anticancer activity. Wogonin induced apoptosis in lung cancer. It was experimented and proved in the nude mouse model [18–20]. It goes through multiple apoptosis pathways such as ROS (Reactive Oxygen Species)-mediated and ER stress-dependent pathway (Figure 5).

2.6. Flavonoid compounds for cancer treatment

2.6.1. Apigenin

Apigenin has anti-mutagenic properties. It inhibits benzo[a]pyrene- and 2-aminoanthracene-induced bacterial mutagenesis. It scavenges free radicals and promotes metal chelation in *in vivo* tumor models [21]. It affords protective effect in murine skin and colon cancer models [22]. It would suppress this enzyme effectively. It also increases glutathione concentration and enhances the endogenous defense against oxidative stress [23]. It was experimented against skin carcinogenesis model. It inhibits dimethylbenzanthracene-induced skin tumors. It has been administered against UV-light-induced cancers. The result showed that it could diminish the occurrence of UV light-induced cancers and was able to increase tumor-free cells. Apigenin plays an effective role to inhibit casein kinase (CK)-2 expression in both prostate and breast cancers [24]. It inhibits HIF-1 α and VEGF expression via PI3K/Akt/p70S6K1 and HDM2/p53 pathways in human ovarian cancer cells [25].

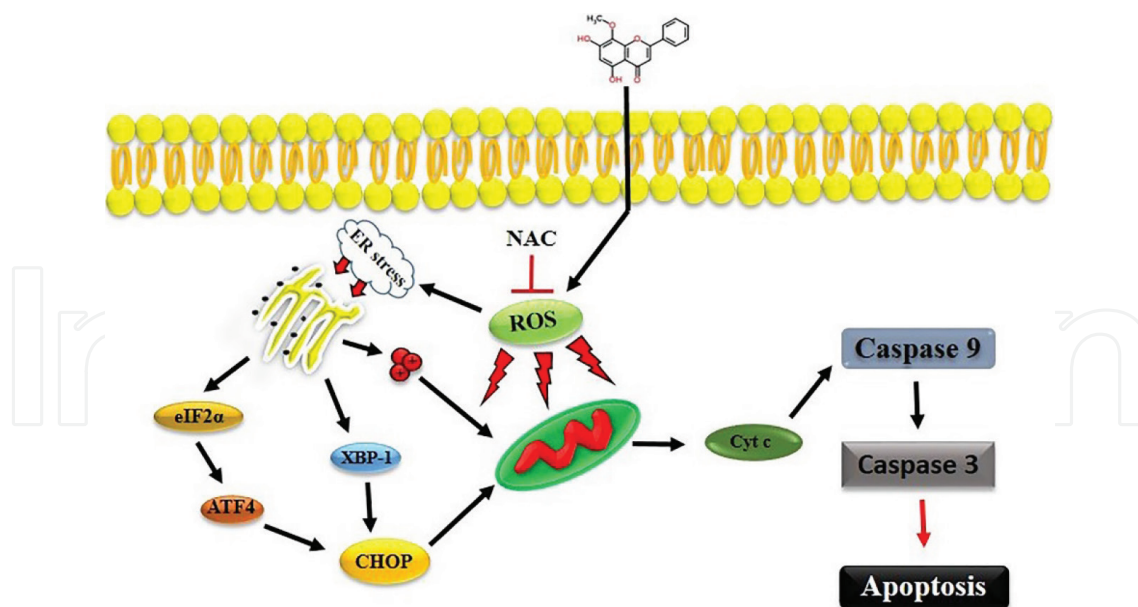


Figure 5. Mechanism of action of wogonin-induced apoptosis in human lung cancer cells. Wogonin induces apoptosis with extrinsic apoptotic pathway and ROS-intervened ER stress-dependent pathway. NAC (N-acetyl-L-cysteine) is used to identify and test ROS. In mammalian cells, the major ER stress sensors such as pancreatic ER kinase (PERK), activating transcription factor-4 (ATF4), ionizing radiation, eIF2 α , and CHOP will carry the signal from the ER lumen to cytoplasm and nucleus in order to recruit ER stress and also to develop tumor progression. Wogonin goes through this pathway and generates apoptosis at the end.

2.6.2. *Kaempferol*

Kaempferol has anticancer effects and acts as a chemopreventive agent. It was found to be curbing the growth of various carcinomas such as glioblastoma (LN229, U87MG, and T98G), leukemia (HL-60 and Jurkat), lung cancer (H460 and A549), breast adenocarcinoma (MCF-7, BT-549, and MDA-MB-231), osteosarcoma (U-2 OS), prostate cancer (LNCaP, PC-3, and DU145), colorectal carcinoma (Caco-2, HCT-116, DLD-1, and Lovo), and pancreatic cancer (MIA PaCa-2, Panc 1). It is used to arrest the cell cycle in cancer cells. It has been used as antiapoptotic agent on cancer cells. Kaempferol is very effective against metastasis and angiogenesis [26].

2.6.3. *Quercetin and diosmin*

Quercetin is one of the dietary flavonoids, which suppresses tumor growth by inhibiting protein tyrosine kinase (PTK). About 10 μ M of this compound confirmed antiproliferative activity against colon cancer cells, Caco-2, and HT-29. Diosmin is one of the important *Citrus* flavonoids, which showed antiproliferative activity in the same cancer cell line. The proliferation of MCF-7 human breast cancer cell line was controlled by the intake of citrus flavones.

2.6.4. *Tangeretin*

Among these phenolic compounds (gallic acid, baicalein, myricetin, 7,3' dimethylhesperetin, quercetin, and luteolin), flavone tangeretin showed better anticancer activity against B16F10, SK-MEL-1 and SK-MEL-5 melanoma cell lines [40, 41], human hepatoma HepG2, Hep3B, and PLC/PRF/5 cell lines [42], HL-60 leukemia cell line [43], and human lung DMS-14 cell line, breast MCF-7 and MDA-MB-435 cell lines, colon HT-29 cell line, and prostate DU-145 cell line [41]. The in vitro studies confirmed that the compound was more effective against various cancer cell lines.

2.7. Anticancer activity of flavonoids

Fruits and vegetables are having an enormous amount of flavonoids, which have been used as cancer chemopreventive agents. Flavonol quercetin is contained in dietary fruits and vegetables especially onion and apple. Quercetin flavonol is used to treat prostate, lung, stomach, and breast cancers [27]. Many biological properties in flavonoids and isoflavonoids are sometimes proved to be cancer chemopreventive. The mechanism of action of flavonoids in the molecular study is cell cycle arrest, heat-shock protein inhibition, tyrosine kinase inhibition, downregulation of p53 protein, estrogen receptor-binding capacity, inhibition of Ras protein, and expression of Ras protein. The most genetic abnormalities in human cancers are based upon p53-mutated proteins. The protein may be downregulated because of flavonoid intake. The flavonoid expression on p53 proteins may lead to arrest cancer cells in G2 and mobile phase of cell cycle. Tyrosine kinases are proteins. They are considered as growth factor signals for the nucleus. The expression of the protein is involved in oncogenesis. The anticancer drug is able to inhibit tyrosine kinase activity. Quercetin has been used in human phase I clinical trial against tyrosine kinase activity. It is proved that it could be considered as antitumor agent without the cytotoxic side effects [28]. It does arrest cell cycle in proliferating lymphoid

cells. Flavonoids inhibit heat-shock proteins in several malignant cell lines, comprising leukemia, colon cancer, and breast cancer [29].

2.8. Antitumor effects

Reactive oxygen species (ROS) can harm DNA and lead to mutations. It is involved in cell signaling and cell growth. It increases the DNA exposure to mutagens. Stefani et al. reported that flavonoids can have inhibition effect against carcinogenesis. Apigenin, fisetin, and luteolin flavonoids have been used to inhibit cell proliferation effectively. A variety of endogenous angiogenic and angiostatic factors have the responsibility for regulating angiogenesis. Flavonoids have the power to fight against angiogenesis. Lumen formation, endothelial cells migration, and their proliferation are the important steps in angiogenesis. Angiogenesis inhibitors can interfere with these steps. Flavonoids play an essential role among the known angiogenesis inhibitors. The inhibition of protein kinases is the possible mechanism for the treatment of angiogenesis. These enzymes are involved in the process of signal transduction against angiogenesis.

2.9. Cancer chemoprevention

Carcinogenesis, the multistep process of tumor development, primarily involves the acquisition of the hallmark capabilities of cancer namely sustaining proliferative signaling, shirking growth suppressors, fighting cell death, triggering invasion and metastasis, and inducing angiogenesis by the incipient cells. Aberrations in multiple intracellular signaling cascades and progressive accumulation of mutations during carcinogenesis present considerable opportunities for the development of clinical interventions in preventing cancer initiation, treating neoplasms during premalignant stages, and inhibiting tumor progression. Natural agents that can target the hallmarks of cancer have attracted the attention of several researchers due to their chemical diversity, structural complexity, inherent biologic activity, affordability, easy availability, and lack of substantial toxic effects. The potential targets of chemopreventive agents include multiple signaling pathways such as ROS generation and signaling, cyclooxygenase-2 (COX-2) and lipoxygenase (LOX) pathways, and numerous cellular molecules like XMEs, transcription factors, proteins involved in cell cycle, apoptosis, invasion and angiogenesis, and enzymes involved in epigenetic modifications.

2.10. Mechanism of action on flavonoids

Flavonoids are proved to be effective chemopreventive agents. The chemopreventive functions of flavonoids are estrogenic/antiestrogenic activity, antiproliferation or apoptosis, prevention of oxidation, induction of cell cycle arrest, regulation of the host immune system, induction of detoxification enzymes, anti-inflammatory activity, and changes in cellular signaling [30]. The research study suggests that the medicinal plant, *Glycyrrhiza inflata* has anticancer activity and also does the mechanism of action on flavonoids. Licorice is the root of *G. inflata* which contains more anticancer properties. Licorice total flavonoids (LTFs) are used effectively against cancer [31].

2.11. Dietary flavonoids on apoptotic pathway

Flavonoids enter through the outer membrane. Bad, Bax, and Bak are the proapoptotic regulators. Bcl-2 and Bcl-x are the apoptosis regulator proteins. Proapoptotic regulators and apoptosis regulator proteins release cytochrome c in the mitochondria (**Figure 6**). Apaf1, dATP, and procaspase-9 are bound with cytochrome c to form the apoptosome. Caspase is activated because of the cleavage of procaspase-9. At the same time, death receptors can interrelate with procaspase-8 to create its active form. A bid can control programmed cell death and can also release cytochrome c. At the end, apoptosis is performed [32].

2.12. Role of intrinsic and extrinsic signaling pathways

The intrinsic and extrinsic signaling pathways are involved in apoptosis. Cellular stress factors are involved in the intrinsic apoptotic pathway. They include ROS generation, endoplasmic reticulum (ER) stress, growth factor deprivation, and ionizing radiation. All these cellular stress factors are responsible for releasing cytochrome c from mitochondria. Apoptosome is the formation of a cytosolic multiprotein complex. It contains the adapter protein apoptotic protease-activating factor 1 (Apaf-1), cytochrome c, and pro-caspase-9.

In the place of apoptosome, caspase-9 begins and activates caspase-3 which cleaves target proteins leading to apoptosis. Pro-apoptotic (e.g., Bax, Bad, Bid, and Bak) and anti-apoptotic (e.g., Bcl-2, Mcl-1, and Bcl-xL) Bcl-2 family proteins have control over this death pathway. The extrinsic pathway is a process whereby the involvement of ligation of a ligand occurs with corresponding receptors. Ligands, such as CD95L, CD95, and TNF, are bound to the corresponding receptors. CD95L [CD95 (Fas/APO-1)-ligand] arbitrates apoptosis. This ligand

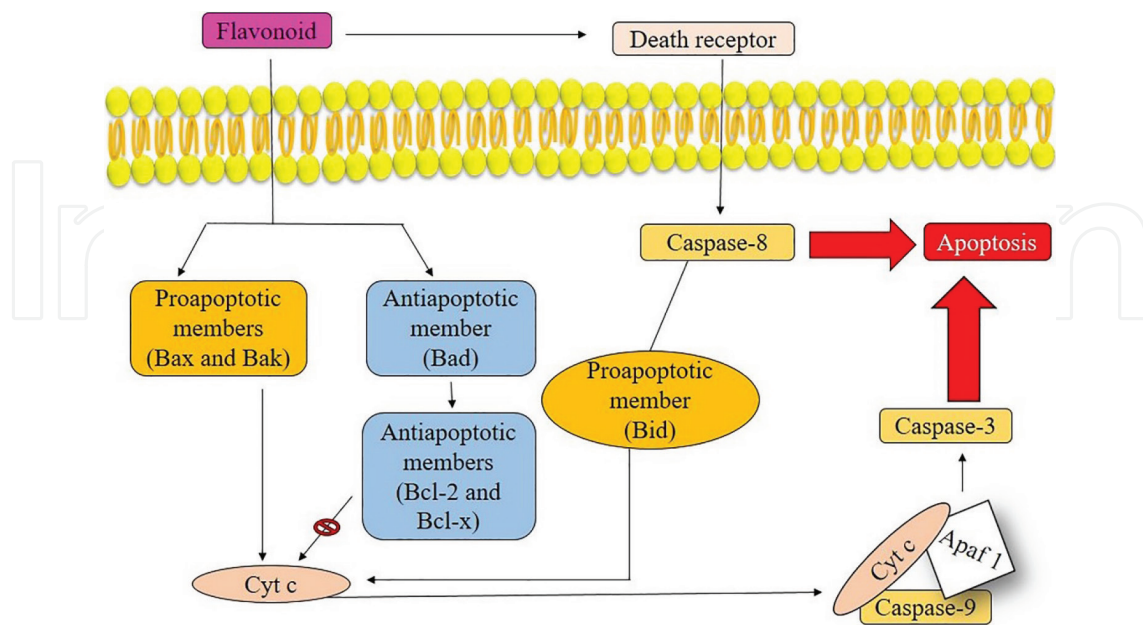


Figure 6. Flavonoids on apoptotic pathway.

binds to the corresponding receptor, CD95 [CD95 (APO-1/Fas)], on the surface of sensitive cells. The corresponding receptor is a prototype death receptor. Fas associated via death domain (FADD), pro-caspase 8, and FLICE-inhibitory protein (FLIP) are collectively called as DISC (death-inducing-signaling-complex). DISC activates caspase-8 which can further activate caspase-3 and leads to apoptosis. One of the other ligands is TNF (tumor necrosis factor). The corresponding receptor is TNF-R. Complex I contains receptor-interacting protein 1 (RIP 1), TNF receptor-associated death domain (TRADD), and telomeric repeat-binding factor 2 (trf 2). It is attached to the receptor itself. Complex II holds RIP 1, TRADD, FADD, and pro-caspase 8. It can be recruited from complex I. The instigation of pro-caspase-8, in turn, activates caspase-3. Mitochondria produce numerous death signals which are needed by the extrinsic death pathway. Caspase 8 activates the extrinsic pathway. It is able to link with an intrinsic pathway. It can also activate the apoptotic gene, Bid. The intrinsic pathway is connected with the apoptotic genes such as Bax and Bak. The above apoptotic gene formation results in cytochrome c. Finally, apoptosis occurs (**Figure 7**).

2.13. *In vivo* and *in vitro* studies on cancer

Quercetin and apigenin can inhibit melanoma cell growth. These compounds have potential to fight against invasive and metastatic cancers. This study has been conducted and proved with mice [33]. *In vitro* studies have confirmed that some flavonoids could inhibit the cell growth of colon, prostate, liver, and breast cancer [34]. Flavonoids can suppress carcinogenesis and also prevent cancer. Thus, these studies confirm the effectiveness of flavonoids in preventing cancer [35].

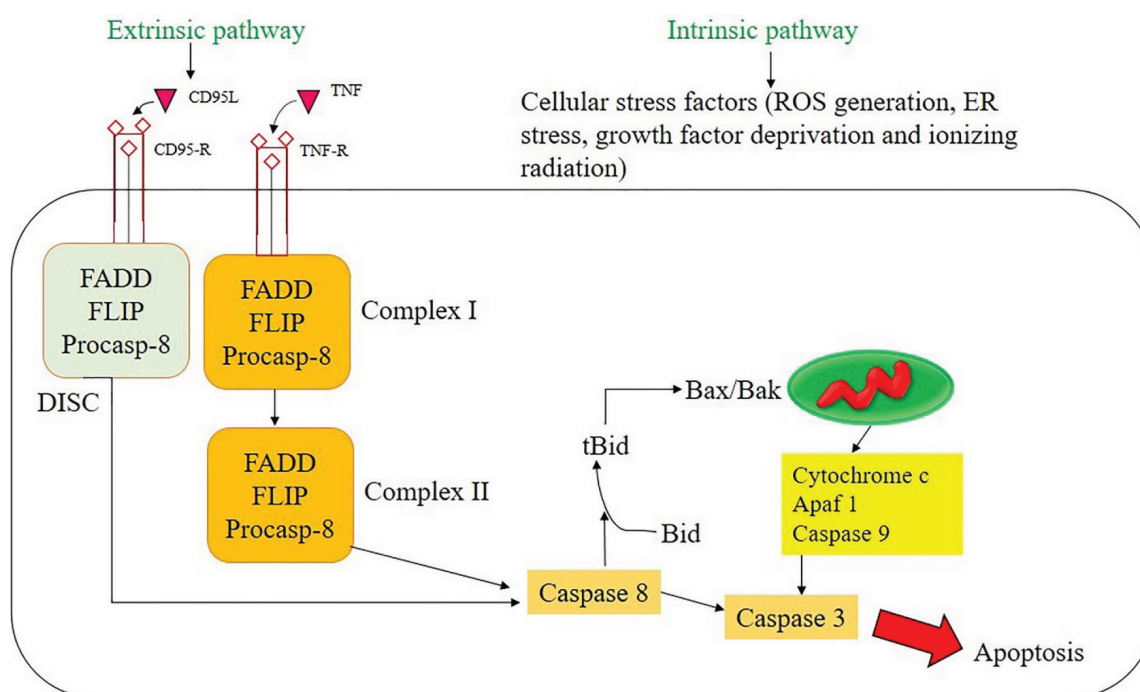


Figure 7. Intrinsic and extrinsic signaling pathways.

2.14. Flavonoids in cancer treatment

Oral cancer was developed chemically and was treated with flavonoids in the rat using 4-nitroquinoline 1-oxide-induced model. It was found later that flavonoid inhibited oral cancer. Kawai et al. studied about some citrus flavonoids and found that they inhibited the proliferation of cancer cells such as lung carcinoma A549 and gastric TGB-C11TKB cancer cell lines. It did not affect the human normal cell lines.

2.15. Cancer process and cancer therapy

Cancer is considered as a genetic illness caused by mutated genes. It is implicated in cell proliferation and cell death. DNA damage may lead to cell death. Three groups of genes are mainly involved in the cancer process. They are oncogenes (damaged proto-oncogenes), the tumor suppressor genes, and the DNA repair genes. Mutated proto-oncogenes lead to oncogenes. They are the responsible genes to proliferate the cells. Tumor suppressor genes code for proteins especially protein p53 and act as checkpoints to cell proliferation or cell death. They can persuade cell cycle arrest in a damaged cell. DNA repair genes can be mutated and lead to a failure in DNA repair [36].

Chemotherapy, radiotherapy, surgery, and some other therapies are available in order to control the risk level of the various cancers and to give a complete cure to the disease. When cancer cells are spread in a human body, chemotherapy is preferred to kill the cancer cells mainly [36].

2.16. Effects of ASMq on TGF- β 1 and TNF- α protein expression

Abnormal Savda Munziq (ASMq), a traditional Uyghur medicine, has anticancer activities. TGF- β 1 and TNF- α protein expression studies are conducted using Western blot. U27 tumor mice model is used for this study. Based on this study, CTX group showed a decreased level of TGF- β 1 and TNF- α proteins. ASMq groups with different dosages expressed decreased TGF- β 1 protein and were increased in TNF- α proteins. Compared to CTX group, TGF- β 1 protein expression of ASMq groups was decreased and protein level was increased in TNF- α [37].

2.17. Definition of cancer prevention

The time period between 2000 and 2006 has witnessed 1.3% of cancer decline among men and the same time period (from 1998 to 2006) has seen 0.5% decline among women. Twenty-five percent of death has also occurred due to the consequence of this disease [38]. The advent of modern technology and its advances have not considerably reduced mortality caused by cancer; it still remains a major threat. As once quipped by Benjamin Franklin, "An ounce of prevention is worth a pound of cure." It is clear that the prevention of the disease is better than the cure. Sporn in 1976 defined cancer chemoprevention as a method "to arrest or reverse premalignant cells." Cancer-chemopreventive capacity of flavonoid is characterized by inhibiting inflammation, scavenging various free radicals, adhesion, suppressing cell proliferation, cell cycle arrest, and apoptosis [39].

2.18. Flavonoids in cancer prevention

A study was conducted on 9959 men and women with regard to consumption of flavonoids and its anticancer activity. It was found that the association between the two was inverse. After some observations, they found that the highest quartile of flavonoid intake reduced the lung cancer up to 50%. Flavonoids can prevent cancers and cure this disease too. Cell cycle arrest happens at G1/S phase, at G2/M, and both phases of G1/S and G2/M phases, and also oxidative radical damages on DNA can be rectified by the dietary flavonoids.

Flavonoids and isoflavonoids are highly antiproliferative, and their compounds come to be handy in curbing the cell cycle or induce apoptosis. They are found to be effective in stopping both G1/S and G2/M of the cell cycle in cultured cancer cell lines. For example, some studies have found that quercetin (30–100 mM) stops the cell cycle at G1/S in human colonic COLO320 DM cells and leukemic T-cells and prompts apoptosis.

2.19. Overview on flavonoids

Flavonoids are commonly nontoxic compounds. They can be used along with synthetic drugs which may have little toxic substances and side effects. The effect of toxic substances in marketed drugs may be decreased due to flavonoid content in the combinational drugs. Therefore, synergistic studies are more effective. Some flavonoids have a chemopreventive effect on nitrosamine-induced carcinogenesis. Many flavonoids protect the genome from chemical carcinogens. Rich anticancer properties are found in various flavonoids which are used to decrease about 20% risk level in cancers. They prevent cancers and also are able to cure the disease. This was proved by *in vitro* and *in vivo* studies.

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