Chapter 9
Flavonoids as Potential Anticancer Agents in Clinics: Where Have We Reached So Far?

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1 Introduction

Cancer is one of the leading causes of mortality, and every sixth death globally is due to cancer. About 8.9 million people died from different types of cancer in 2016. According to a recent report, the majority of deaths in cancer patients are predominantly due to cancer of the prostate, colorectum, breast, and lungs (Siegel et al. 2017). Even with the progress in the discovery of novel anticancer medications, cancer is still the leading cause of mortality worldwide (May 2014; Siegel et al. 2017). There is an increased incidence of cancer along with the unwanted side effects of chemotherapeutic agents. This has enforced the scientists to explore the future anticancer agents from natural sources. Notably, plant-derived anticancer agents have gained attention because of their low toxicity and better therapeutic efficacy (Pan et al. 2013). The plant-derived drugs have diverse mechanisms of action, but most of them cause apoptotic cell death by caspase or p53-dependent as well as p53-independent mechanisms. In addition, plant-derived drugs exhibit their anticancer activity through certain novel mechanisms such as autophagy, mitotic catastrophe, and senescence leading to cell death and necrosis-like programmed cell death (Gali-Muhtasib et al. 2015).

Plants synthesize a wide array of chemical compounds like flavonoids, alkaloids, glycosides, terpenoids, etc. Many of these compounds are produced by plant as

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secondary metabolites, which help the plants to respond against various environmental stimuli and stresses as well as genetically programmed developmental signals. It is estimated that more than 50% of modern pharmaceuticals have originated from the plant sources. In the recent times, there is an increasing contemplation in the scientific community about the importance of phytomedicines, phytochemistry, and pharmacological investigations of natural health products and diets for treating noncommunicable diseases, especially cancer, type 2 diabetes, obesity, cardiovascular, and neurodegenerative disorders. Partly, this is due to the realization that in folklore medicine, herbal remedies have been used effectively for treating different ailments. At present, there exists data from an overwhelming number of in vitro and in vivo studies showing beneficial effects of plant-based extracts and their bioactive ingredients. Many clinical studies with isolated ingredients from plants have revealed multiple health benefits in boosting immune function, anti-inflammation, antimicrobial, and antioxidant activities.

Flavonoids are polyphenolic substances, which are widely found in fruits, vegetables, and certain beverages. They are associated with various therapeutic activities and are present in various nutraceutical, pharmaceutical, medicinal, and cosmetic preparations. The basic structure of flavonoid contains flavan nucleus having 15 carbon atoms arranged in three rings (C_6–C_3–C_6). The various classes of flavonoids exist as flavones (e.g., apigenin and kaenpteral), flavanones (e.g., hesperetin and fisetin), catechins (e.g., catechin and epigallocatechin gallate), and anthocyanins (e.g., cyanidin and delphinidin). The basic nucleus of flavonoid and its various subtypes is given in Fig. 9.1. In addition, the various food sources of various types of flavonoids are summarized in Table 9.1.

2 Flavonoids as Pharmacological Agents

Several types of flavonoids, flavanols, flavones, and flavanonols isolated from plants, vegetables, and fruits have shown multifarious biological activities, such as antioxidant, anti-inflammatory, antidiabetic, cardioprotective, as well as anticancer activity. Various pharmacological activities of flavonoids are depicted in Fig. 9.2.

3 Flavonoids as Anticancer Agents

3.1 Flavanols

3.1.1 Myricetin

Myricetin is a phenolic compound isolated from *Myrica nagi* Thunb. bark belonging to family Myricaceae (Lau-Cam and Chan 1973). It is found mostly in vegetables, berries, wines, and teas prepared from different plants mainly from families

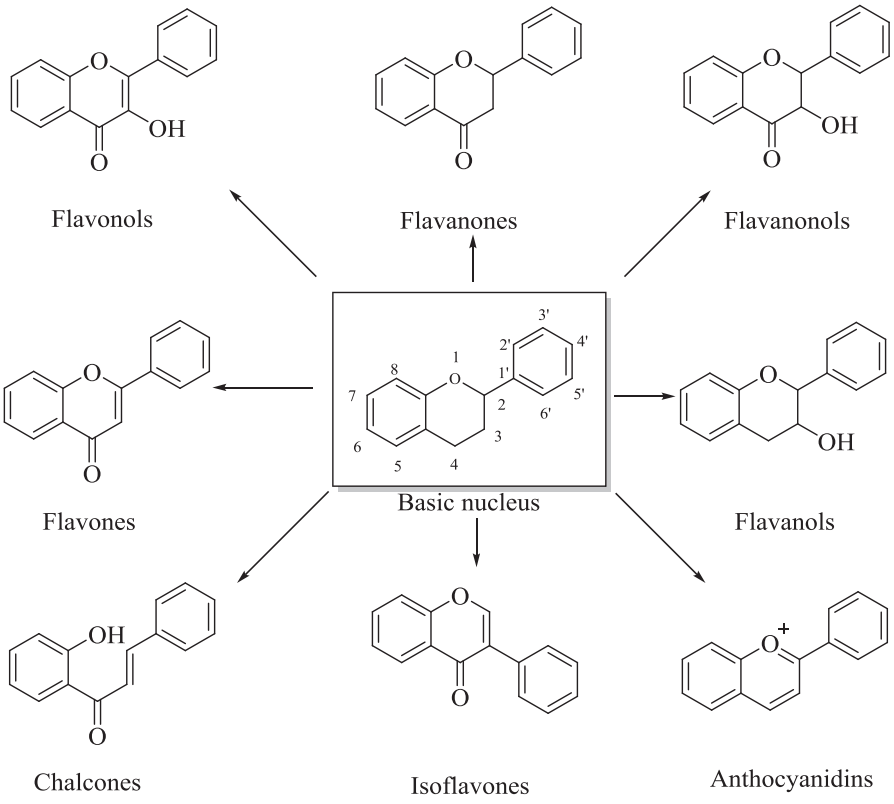


Fig. 9.1 Chemical structures of various types of flavonoids

Primulaceae (Chua et al. 2011), Polygonaceae (El-Kader et al. 2013), Myricaceae (Jones et al. 2011), Pinaceae (Hergert 1956), and Anacardiaceae (Umadevi et al. 1988). It is 3,5,7-trihydroxy-2-(3,4,5-trihydroxyphenyl)-4-chromenone and occurs in free and bound form such as myricetin-3-O-(4″-acetyl)-α-L-arabinopyranoside, myricetin-3-O- β-D-xylopyranoside, myricetin-3-O-(3″-O-galloyl)-α-L-rhamnoside, etc. (De Leo et al. 2006; Kong et al. 2014). Myricetin exhibits its anticancer activity against several types of cancers. Myricetin affects Akt signaling in EGF-induced cell transformation by competing with ATP and thereby inhibits the expression of Akt. Thus, it is demonstrated that myricetin is an inhibitor of Akt which is overexpressed in the cancer cells. Moreover, it inhibits the cancer cell growth by inhibiting their entry into mitotic phase by targeting the kinase activity of cyclin B/CDK1 complexes. Studies suggest its antimitotic potential in treating liver cancer and its apoptotic cell death-promoting activity in various cell lines. In addition, myricetin targets the tumor metastasis and angiogenesis mechanisms by targeting several proteins including MMP-9, MMP-13, VGEF, and HIF-1 (Devi et al. 2015).

Table 9.1 Food sources of different flavonoids

Groups	Compounds	Food sources
Flavanols	Isorhamnetin Kaempferol Myricetin Quercetin Quercetagetin	Apple, black grapes, blueberry, broccoli, cherry, curly kale, green and black tea, leek, tomato, yellow onion
Flavones	Apigenin Chrysin Diosmetin Heptamethoxyflavone Nobiletin Luteolin Quercetagetin Sinensetin Tangeretin Tricetin	Capsicum pepper, celery, parsley
Flavanones	Dihydrofisetin Dihydroquercetin Eriodictyol Hesperetin Naringenin Dihydrobinetin	Grapefruit juice, lemon juice, orange juice
Flavanols	Pinobanksin Silibinin Silymarin Taxifolin	Chocolates, cocoa beverages, cocoa
Catechins (proanthocyanidins)	(−) Epicatechin (+) Catechin Epicatechin-3-gallate Epigallocatechin Epigallocatechin-3-gallate Gallocatechin	Apricot, beans, black tea, blackberry, cherry, chocolate, cider, grapes, green tea, peach, red wine
Isoflavones	Daidzein Genistein Glycitein	Soy bean, soy cheese, soy flour, tofu
Anthocyanins	Cyanidin Delphinidin Malvidin Pelargonidin Peonidin Petunidin	Black grapes, blackcurrant, blue berry, cherry, plum, red cabbage, red wine, rhubarb, strawberry

3.1.2 Quercetin

Quercetin (3,3,4,5,7-pentahydroxy flavanone) is a unique bioflavonoid found abundantly in fruits and vegetables such as grapes, tomatoes, *Brassica* vegetables, onions, and tea (Häkkinen et al. 1999; USDA 2011). Reports suggest that quercetin in combination with many naturally occurring compounds such as luteolin

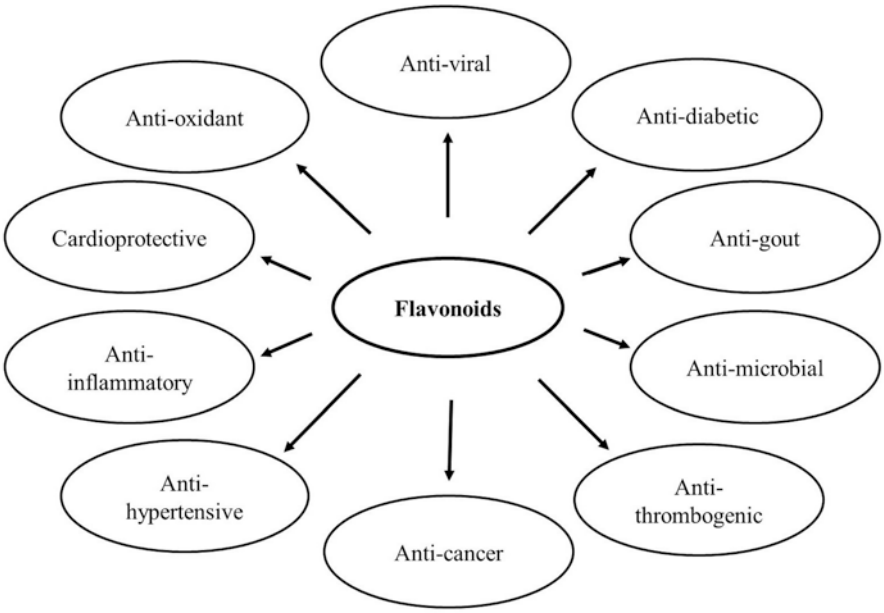


Fig. 9.2 Illustration of multifarious biological activities of flavonoids

derivatives, resveratrol, 2-methoxyestradiol, ellagic acid, and synthetic drugs like cisplatin and doxorubicin resulted in synergistic anticancer activity (Akagi et al. 1995; Mertens-Talcott and Percival 2005; Nessa et al. 2011; Wang et al. 2012; Yang et al. 2015).

Quercetin modulates the cell signaling by inhibiting the high-mobility group box protein 1 (HMGB1)-induced TNF-α and IL-1β expression, which further regulates activity of various pro-inflammatory cytokines (Degryse et al. 2001). Furthermore, quercetin considerably inhibits the degradation of IκBα and nuclear translocation of NF-κB which is important for cytokine expression (Park et al. 2004; Kokkola et al. 2005). Quercetin has been demonstrated to prevent metastasis of breast cancer cells through suppression of matrix metalloproteinase-9 (MMP-9) in 12-O-tetradecanoyl phorbol-13-acetate (TPA)-treated MCF-7 cells (Lin et al. 2008). Oral administration of quercetin encapsulated with tamoxifen in PLGA nanoparticles significantly increased its bioavailability and attenuated breast cancer cell growth through induction of apoptosis (Jain et al. 2013).

3.1.3 Resveratrol

Resveratrol (3,5,4′-trihydroxystilbene) is a naturally occurring polyphenol belonging to stilbenes. It is found mostly in peanuts, berries, grapes, and plant sources and also in red wine (Bielsalski 2007). In plants, resveratrol exists in two isomeric

forms, i.e., *trans*-resveratrol and *cis*-resveratrol, and their glucosides, *trans*-piceid and *cis*-piceid. The anticancer potential of resveratrol was first published in 1997 (Jang et al. 1997).

Research reports suggest that resveratrol downregulates the K_{ras} expression, prevents the formation and progression of colorectal tumors, and increases the expression of miR-96 (Saud et al. 2014). Furthermore, it also modulates the mitomycin C-mediated effects of colorectal cancer by inhibiting cell growth and upregulating p21 which blocks cell cycle at G0/G1 and G2/M phases (Ali and Braun 2014). It further regulates the metabolism of glucose and regulates GLUT1 in ovarian cancer cell lines. Resveratrol suppresses glucose uptake and inhibits plasma membrane GLUT1 localization linked with the inhibition of the activity of Akt in ovarian cancer cell lines (Gwak et al. 2015).

In a clinical trial study, Patel and his colleagues demonstrated that in colon cancer patients, resveratrol at dose levels of 0.5 and 1.0 g reduces tumor cell proliferation by 5% (Patel et al. 2010). In an another study, Brown et al. showed that resveratrol causes a decrease in circulating insulin-like growth factor (IGF)-I and IGF-binding proteins (IGFBP)-3 in healthy volunteers (Brown et al. 2010). This study demonstrated that resveratrol may affect the IGF axis probably by direct effect on IGF-I and IGFBP-3. These proteins may also serve as potential markers in chemopreventive efficacy in human clinical trials (Jogie-Brahim et al. 2009) (Fig. 9.3).

3.2 Flavones

3.2.1 Luteolin

Luteolin or 3′,4′,5,7-tetrahydroxyflavone is a flavonoid present in various fruits, vegetables, as well as medicinal herbs. Traditional Chinese medicine has used luteolin-rich herbs as anti-inflammatory and anticancer agent. These biological effects of luteolin are attributed to antioxidant or pro-oxidant activity (Lin et al. 2008). Luteolin has been noted to kill various types of cancer cells including leukemia, pancreatic tumor, hepatoma, and lung carcinoma (Huang et al. 1999; Lee et al. 2002, 2005; Cheng et al. 2005). Luteolin has been demonstrated to serve as anticancer agent by inhibiting cell proliferation, metastasis, angiogenesis, and induction of

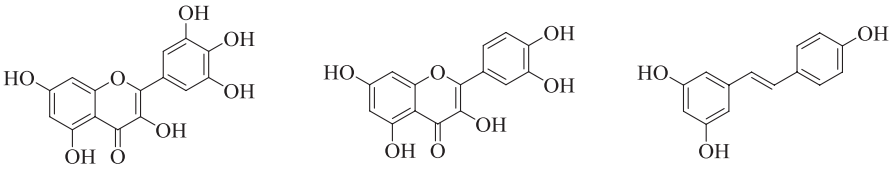


Fig. 9.3 Chemical structure

apoptosis. Luteolin promotes cytotoxicity in cancer cells by suppressing survival mechanisms such as PI3K/Akt pathway and stimulating the tumor suppressor p53 signaling (Han et al. 2002). Luteolin suppressed the cancer stem cell properties and their metastatic potential in prostate cancer cells (Tsai et al. 2016). Luteolin inhibits the human cytochrome P450 (CYP) 1 enzymes including CYP1A1, CYP1A2, and CYP1B1, which further suppress the activation of carcinogens (Kim et al. 2005). In vascular smooth muscle cells, luteolin inhibited the PDGF-mediated proliferation of endothelial cells and consequently inhibited the PDGF-induced activation of ERK, PI3K/Akt, and PLC-1 along with reduction of c-fos gene expression (Kim et al. 2005). Moreover, luteolin promotes JNK-mediated apoptosis by modulating bad or p53 pathways (Yu et al. 2004; Ju et al. 2007). Notably, JNK-mediated p53 activation governs the expression of Bax, which further regulates apoptosis (Yu et al. 2004). Luteolin has been demonstrated to induce endoplasmic reticulum stress and mitochondrial dysfunction which leads to apoptosis in gliomablastoma (Wang et al. 2017). Luteolin treatment induced G_0/G_1 phase arrest in SMMC-7721 hepatocarcinoma cell line. Luteolin promoted autophagy by increasing number of intracellular autophagosomes in cancer cells. Interestingly, chloroquine, an autophagy inhibitor, attenuated the anticancer effect of luteolin in hepatocarcinoma cell line (Cao et al. 2017). Another novel mechanism suggested for anticancer potential of luteolin is blockage of ribosomal S6 kinase (RSK). RSK is ERK regulated and is responsible for cell growth and its survival. Luteolin treatment blocked RSK-1 and demonstrated marked anticancer potential in MOLM-13 and Kasumi-1 leukemic cells (Deng et al. 2017). Luteolin inhibited the incidence rate of tumors and decreased tumor volume in 7,12-dimethylbenz(a)anthracene (DMBA)-induced mammary carcinogenesis in rats (Samy et al. 2006). In another study, luteolin reduced DMBA-induced lung carcinogenesis in mice (Kasala et al. 2016). An early phase I clinical trial is under process to examine whether luteolin and nano-luteolin exert an inhibitory effect on tongue squamous cell carcinoma cell lines by inducing apoptosis and to assess if nano-luteolin has more efficient apoptotic activity than luteolin on tongue squamous cell carcinoma cell line (https://clinicaltrials.gov/ct2/show/NCT03288298).

3.2.2 Diosmetin

Diosmetin (3′,5,7-trihydroxy-4′-methoxyflavone) is the aglycone part of the flavonoid glycoside diosmin (3′, 5, 7-trihydroxy-4′-methoxyflavone-7-aminoglycoside) which occurs naturally in the genus *Teucrium* (Lamiaceae) and in Portuguese olive leaves (Meirinhos et al. 2005; Macedonia 2005; Spanakis et al. 2009). Intestinal microflora enzymes hydrolyze diosmin to its aglycone diosmetin before its absorption into the body (Kanaze et al. 2004). Pharmacologically, it has been established that diosmetin possesses different medicinal properties such as antimicrobial, antioxidant, anti-inflammatory, as well as anticancer activities (Chandler et al. 2010; Domínguez et al. 2011; Zhao et al. 2011). In a study, diosmetin is identified as a CYP1 substrate (Androutsopoulos et al. 2009a). CYP1A1 is one of the cytochrome

P450 enzymes, which has been extensively examined for its capacity to activate compounds having carcinogenic potential. The exposure to environmental carcinogens is noted to increase the level of CYP1A1 expression through aryl hydrocarbon receptors. Diosmetin treatment inhibited cell proliferation of the human breast adenocarcinoma MCF-7 cells which were pre-induced with the potent CYP1 inducer 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) (Androutsopoulos et al. 2009a). Diosmetin inhibited the proliferation and progression of cell cycle in MDA-MB 468 cells by affecting CYP1 enzyme, whereas it had no aversive effect on normal breast cell lines MCF-10A. This shows its safety of use over other synthetic drugs. Diosmetin is also reported to induce G1 arrest in MDA-MB-468 cell lines. Interestingly, it is proclaimed that the diosmetin is metabolized to similar flavone luteolin in MDA-MB-468 breast cancer cell lines selectively through aromatic demethylation of the B ring by CYP1A1, CYP1B1, and the hepatic enzyme CYP1A2, which is not seen in MCF-7A cells (Androutsopoulos et al. 2009b).

3.2.3 Nobiletin

Nobiletin (5,6,7,8,3′, 4′-hexamethoxyflavone) is a major component of *Citrus depressa* and is noted to exhibit anticancer activity in various in vitro and in vivo studies. Literature reveals that nobiletin inhibits the proliferation of skin, breast, prostate, and colon carcinoma cell lines (Kandaswami et al. 1991). It inhibits the production of matrix metalloproteases which results in antiproliferative activity (Ishiwa et al. 2000). Nobiletin inhibits the invasion of human fibrosarcoma HT-1080 cells by suppressing the metalloproteinases and activating TIMP-1 production. Nobiletin inhibits the phosphorylation of mitogen-activated protein/extracellular signal-regulated kinase-1/2 (MEK-1/2). Notably, U0126, a MEK1/2 inhibitor, imitated the nobiletin's action to reduce ability to decrease 12-O-tetradecanoyl phorbol-13-acetate (TPA)-stimulated production of proMMPs-1 and proMMPs-9 in human fibrosarcoma HT-1080 cells (Miyata et al. 2004). Moreover, in TPA-treated HT-1080 cells, nobiletin assisted the phosphorylation of c-Jun NH_2-terminal kinase (JNK), which is an important downstream signal factor of the PI3K/Akt pathway. Among 40 different flavonoids, nobiletin showed the maximum antiproliferative activity in six human cancer cell lines (Murakami et al. 2000; Manthey and Guthrie 2002). It suppresses the prostaglandin E_2 (PGE_2) production and cyclooxygenase-2 expression in in vitro studies (Kohno et al. 2001). Studies demonstrated that administration of nobiletin-rich *C. Reticulata* peel extract for 1 year exhibits preventive effects on the progression of the cognitive impairment in donepezil-pre-administered Alzheimer disease patients without any side effects. Unfortunately, the research on nobiletin clinical application is quite limited, which might be due to the uncertainty of molecular targets. More clinical trials of nobiletin and its metabolites are still needed.

3.3 Flavanones

3.3.1 Hesperidin

Hesperidin (5,7,3′-trihydroxy-4′-methoxy-flavanone 7-rhamnoglucoside) belongs to the class of flavonoids called flavanones and is predominantly found in citrus fruits. Hesperidin has been noted to possess a diverse range of pharmacological activity attributing to its anti-inflammatory and antioxidant potential. In the last few years, hesperidin has gained attention of cancer biologists, and it has been screened extensively in vitro and in vivo for its antimutagenic and anticancer properties. In the endometrial cancer cells, hesperidin induced apoptosis by increasing Bax and decreasing Bcl_2 and promoted cell death by downregulating estrogen receptor I (Cincin et al. 2018). Hesperidin has been noted to mitigate the migration and invasion of A549 cancer cells by inhibiting SDF-1/CXCR-4 cascade (Xia et al. 2018b). Hesperidin has been demonstrated to suppress azoxymethane-induced colon carcinogenesis in rats (Tanaka et al. 1997). Interestingly, hesperidin administration along with doxorubicin has been reported to increase laters' anticancer activity along with reduction in its side effects in Ehrlich ascites carcinoma-bearing mice (Donia et al. 2018). Hesperidin treatment demonstrated anticancer activity by inducing endoplasmic reticulum stress and G_0/G_1 arrest in ovarian cancer cell line and A549 lung cancer cell line, respectively (Zhao et al. 2017; Xia et al. 2018a). Hesperidin attenuated diethylnitrosamine/carbon tetrachloride-induced hepatocarcinogenesis in rats through activation of PPAR-γ and Nrf-2/ARE/HO-1 signaling (Mahmoud et al. 2017). Notably, hesperidin demonstrated better cytotoxic activity against human hepatic cancer HepG2 cell line than other flavonoids such as neohesperidin, naringin, and naringenin. Moreover, hesperidin has been noted to induce apoptosis in HepG2 cells through mitochondrial as well as death receptor pathway (Banjerdpongchai et al. 2016). Hesperidin has been noted to upregulate tumor suppressor phosphatase and tensin homologue (PTEN) and reduce the expression of PI3K/Akt survival pathway in azoxymethane-induced colon carcinoma in mouse. Moreover, hesperidin-mediated restoration of glycogen beta-synthase-3 attenuated the proto-oncogenes such as c-jun, c-myc, and β-catenin, thereby resulting in anticancer activity in colon cells (Saiprasad et al. 2014) (Figs. 9.4 and 9.5).

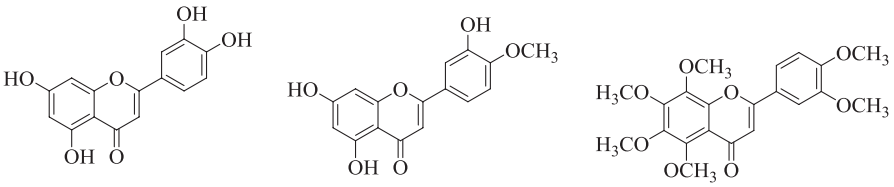
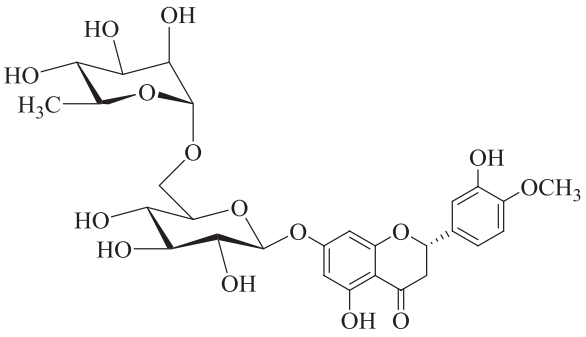


Fig. 9.4 Chemical structure

Fig. 9.5 Chemical structure



Hesperidin

3.4 Flavan-3-Ols

3.4.1 Epigallocatechin-3-Gallate

Green tea is extracted from the leaves of evergreen shrub *Camellia sinensis* and is almost consumed all over the world (Yang et al. 2009). Green tea mainly contains polyphenols and catechins such as epigallocatechin-3-gallate (EGCG), epicatechin-3-gallate, epigallocatechin (EGC), and epicatechin (EC). Among all the above catechins, epigallocatechin-3-gallate (EGCG) possesses powerful anticancer activity due to its antioxidative potential (Katiyar and Mukhtar 1996). EGCG is the ester form of epigallocatechin and gallic acid. EGCG has also been reported to have beneficial effects in the treatment of neurodegenerative diseases (Hügel and Jackson 2012), cardiovascular diseases (Tipoe et al. 2007), cancer (Schramm 2013), diabetes (Thielecke and Boschmann 2009), and liver diseases (Xiao et al. 2014).

EGCG inhibits tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced lung tumorigenesis by inhibiting 8-hydroxydeoxyguanosine formation (Xu et al. 1992). Furthermore, it inhibits dimethylarsinic acid and cisplatin-induced lung tumorigenesis in rodent models (Mimoto et al. 2000; An et al. 2008) and diethylnitrosamine-induced liver tumorigenesis by inhibiting insulin-like growth factor signaling in diabetic and obese C57BL/KsJ-db/db mice (Shimizu et al. 2011). EGCG inhibits angiogenesis and tumor growth in human pancreatic cancer and breast cancer by downregulating VEGF expression both in serum-deprived HT29 human colon cancer cells and in vivo (Jung et al. 2011; Shankar et al. 2013; Braicu et al. 2013). Moreover, EGCG inhibits invasion and metastasis in hypopharyngeal carcinoma cells by downregulating hepatocyte growth factor (HGF)-induced MMP-9 as well as activation of urokinase-type plasminogen activator (uPA) (Lim et al. 2008).

The consumption of green tea exerts beneficial effects even after a single dose. The levels of prostaglandin E2 (stimulates colorectal carcinogenesis) in tissue were reduced in normal subjects after 4 h of green tea consumption (August et al. 1999). The derivatives of green tea have shown effectiveness against various malignancies such as cervical, hepatic, and prostate, without toxicity in patients with premalignant conditions (Ahn et al. 2003; Bettuzzi et al. 2006; Luo et al. 2006). However, in a phase

2 clinical trial of China, there is no marked effect observed in biomarkers of esophageal squamous carcinogenesis from decaffeinated green tea (Wang et al. 2002).

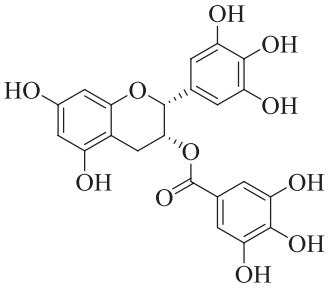
In a single-arm trial testing, the effectiveness of EGCG against radiation-induced dermatitis in the patients of breast cancer demonstrated promising results. Topical application of EGCG reduces the pain in 85.7%, itching in 87.8%, tenderness in 79.6%, and burning feel in 89.8% patients, who underwent radiotherapy (Zhu et al. 2016). In a phase II clinical trial, EGCG treatment ameliorated the acute radiation-induced esophagitis (ARIE) in patients with stage III lung cancer. ARIE is one of the dose-dependent toxicities complicated by thoracic radiotherapy (Zhao et al. 2015). The supplementation of green extract having high concentration of EGCG for 12 months showed no observed change in the mammographic density in all postmenopausal women, but a marked reduction in percent mammographic density (PMD) was observed in 50–55-year-old women suggesting the effectiveness of green tea supplementation in preventing breast cancer (Samavat et al. 2017). The use of EGCG in bladder cancer in patients has demonstrated prosperous result in phase II clinical trial (Gee et al. 2017) (Fig. 9.6).

3.4.2 Pomegranate-Derived Polyphenols

Punica granatum is a small tree of family Punicaceae, commonly known as pomegranate. The fruits of the plant are used in many cultures. Of note, the name *Punica* has been derived from the Roman name of city Carthage, where best pomegranates have been known to grow. This tree is native to Persia but is now cultivated in America, Mediterranean area, and Asia. A class of tannins known as punicalagins unique to pomegranates has been demonstrated to possess excellent free radical scavenging properties (Gil et al. 2000; Noda et al. 2002).

Scientific reports suggest the potential role of pomegranate in the prevention as well as treating various types of cancer such as skin cancer, lung cancer, breast cancer, and prostate cancer because of its antioxidant nutrients. It slows down the propagation of cancer cells and accelerates their death. It also diminishes the blood supply to tumors and makes them smaller by starvation (Adhami et al. 2009).

Fig. 9.6 Chemical structure



Epigalocatechin-3-gallate

Polyphenols obtained from the fermented juice and pericarp of pomegranate inhibit the proliferation and invasion of cells by inhibiting the secretory phospholipase (Lansky et al. 2005; Seeram et al. 2007; Espín et al. 2007). Standardized pomegranate extract having ellagitannins and ellagic acid suppresses the expression of androgen receptor through the inhibition of androgen-synthesizing enzymes. Moreover, pomegranate juice or extract inhibits the CYP enzyme, induces apoptosis and inhibits tumor growth, and decreases the serum PSA levels (Malik et al. 2005; Espín et al. 2007; Rettig et al. 2008; Paller et al. 2013). In skin cancer, it protects the fibroblasts from cell death and facilitates the skin repair (Aslam et al. 2006; Pacheco-Palencia et al. 2008; Hayouni et al. 2011). It also inhibits the skin edema, hyperplasia, and leukocytic infiltration induced by UV-B (Afaq et al. 2010; Khan et al. 2011).

In a human study, drinking of 8 oz. pomegranate juice per day increased the amount of time it took for their prostate-specific antigen (PSA) to double in patients who had surgery or radiation therapy for treating prostate cancer. Notably, the patients doubling PSA levels a short period of time have more risk of getting prostate cancer. Daily consumption of pomegranate juice increased the time of PSA levels to double from about 15 months to 54 months (Hajleh and Al-Dujali 2016).

3.5 Isoflavones

3.5.1 Genistein

Genistein (4′,5,7-trihydroxyisoflavone) was originally isolated from *Genista tinctoria* Linn. (Dyer's broom) in 1899. It is predominant isoflavone of soy products (Perkin and Newbury 1899). Genistein structurally resembles estrogen, and therefore isoflavones have also been known as phytoestrogens. Genistein can thus bind to estrogen receptors due to structural similarity (Kuiper et al. 1997). It is documented that genistein can inhibit the growth of various cell lines such as prostate, leukemia, lymphoma, breast, lung, head, and neck cancer cells both in vitro and in vivo (Taylor et al. 2009). Various studies have reported the role of genistein as anticancer in every step of tumor progression. Genistein has been noted to attenuate the growth of cancer cells by inhibiting PTK-mediated signaling pathways (Akiyama et al. 1987; Sakla et al. 2007). It also exerts its inhibitory effect on all steps of cancer progress through apoptosis and cell cycle arrest, regulating the AKT/IKK/NF-κb, androgen mediated and other signaling pathways in the development of carcinogenesis. Studies showed that genistein modulates the expression of genes that regulates cell cycle and growth and thereby inhibits progression of cancer (Pavese et al. 2010).

Genistein is an isoflavone, which means its B ring is attached to the heterocyclic ring at the C3 position instead of C2 (Jacob, Hagai and Soliman 2011). It is a prominently found in soy products, (Herman et al. 1995; Barnes 1995). It inhibits cancer cell growth and induces apoptosis by modulating the expression of genes related to apoptotic pathways and inhibits Akt activation and NF-κB in cancer cells (Li et al. 1999; Davis et al. 1999). Genistein inhibits the invasive potential of human prostate cancer cell lines which suggest that it could inhibit the metastatic growth of

prostate cancer (Santibanez et al. 1997). The in vitro studies using microarray shown that the genistein regulates the expression of genes involved in angiogenesis, cell cycle, cell growth, cell signal transduction, metastasis, and tumor cell invasion (Li and Sarkar 2002). In targeting the breast cancer, genistein possesses higher affinity toward ERβ subunit of estrogen receptor (ER) comparable to other isoflavones. This is attributed to the presence of a phenolic hydroxyl group, which is required for the formation of an intramolecular hydrogen bonding. The low concentrations of genistein (EC_{50} 4 nM) overexpress gene expression and reduce proliferation more efficiently when ERβ is present. At higher doses, it stimulates the proliferation of MCF7/ERα cells which is counted as bad effects. At the end of 30-day clinical trial on adults, early-stage breast cancer patients (mainly HER2-negative and ER-positive), those with soy supplementation and high plasma genistein, had overexpression of tyrosine kinase receptor FGFR2 and other genes regulating proliferation pathways and cell cycle (Shike et al. 2014).

Genistein inhibited the HER2 expression, phosphorylation, and promoter activity through ER-independent manner (Sakla et al. 2007). MDA-MB-231 cell lines treated with varying concentrations (5–10–20 μM) of genistein demonstrated induction of apoptosis and G2/M cell cycle arrest in a dose as well as time-dependent manner. This effect is due to genistein inhibition of NFκB through NOTCH-1 signaling, which affects Bcl-2 and Bcl-xl expression as a consequence of NFκB inhibition (Pan et al. 2012). In a phase 2 chemoprevention trial on bladder cancer, the daily oral dose of genistein (300 mg/day and 600 mg/day) for 14–21 days before the surgery targets p-EGFR (endothelial growth factor receptor). The difference between p-EGFR staining of placebo arm and genistein arm is significantly different in 300 mg/day group but not in 600 mg/day (Messing et al. 2012). Genistein displayed a possible bimodal effect on bladder cancer tissue EGFR phosphorylation. Phase 2 studies of genistein were conducted in patients with prostate cancer. In this study, before undergoing radical prostatectomy for localized prostate cancer, patients were randomized to treatment with 2 mg genistein per kg of body weight versus no treatment (Xu et al. 2009). Normal prostate epithelial cells were excised selectively from prostate tissue by laser capture microdissection after the treatment, and these cells represent an "at-risk" target-type cells which are decent target for compound which arrests the conversion to an invasive phenotype. The qRT-PCR used to measure levels of MMT-2 transcript demonstrated that genistein reduced the MMT-2 gene expression to 24% of the level observed in control subjects. This study establishes the possibility of inhibiting prometastatic processes through a targeted therapeutic intervention in human subjects (Xu et al. 2009). In another phase 2 trial, patients having progressive prostate cancer when treated with soy milk for 12 months 3 times a day reduced the rise in PSA antigen as compared to its increase in patients before entering the study. Moreover, in a third phase 2 trial of genistein, men with prostate cancer were administered soy extract for 6 months, and it was concluded that the therapy was well tolerated with less than 10% patients experiencing mild diarrhea, and in 17% of patients, there was reduction of PSA levels (deVere White et al. 2004; Pendleton et al. 2008). Administration of genistein has been noted to influence various genes responsible for cell proliferation in randomized double-blind clinical trial of patients with localized prostate cancer (Bilir et al. 2017).

Moreover, treatment with AXP107-11 (the crystalline form of genistein) in phase I trial of pancreatic cancer patients in combination with gemcitabine demonstrated a favorable pharmacokinetic profile along with its increased bioavailability without any toxicity (Lohr et al. 2016) (Fig. 9.7).

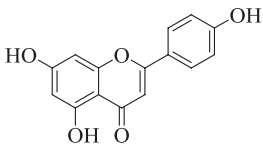
3.6 Anthocyanins

3.6.1 Cyanidin

Anthocyanins are widely distributed in human diets and are used for food color, suggesting that we ingest the considerable amount of anthocyanins from plant-based daily diets. In six different tumor cell lines (K562, PC3, HT-29, M-14, MCF-7, and DU145), it effectively halted the growth of cancer cells at lower GI_{50} concentrations than quercetin (Murphy et al. 2003). Cyanidin significantly attenuated zymosan-mediated inflammation in rodents. It suppressed the peritoneal exudates, tumor necrosis factor-α (TNF-α) interleukin-1 β (IL-1β) and IL-6, and cytokine-induced neutrophil chemoattractant-1 protein (CINC-1) levels (Tsuda et al. 2002). The zymosan elevated serum-α_2-macroglobulin, and decrease in serum albumin and transferrin level was corrected by cyanidin in vivo. Ingestion of cyanidin-3-glucoside (C3G) in Apc^{Min} mice reduced the intestinal adenomas in a dose-dependent manner (Cooke et al. 2006). Total C3G concentration in mice was 43 ng/g and 8.1 μg/g tissue, respectively, in the intestinal mucosa and 7.2 and 12.3 μg/ml in the urine (Cooke et al. 2006). In a ^{13}C-tracer clinical trial, total eight participants consumed 500 mg isotopically labeled C3G (6,8,10,3′,5’-$^{13}C_5$-C3G). The maximal elimination rate of C3G is seen after 6–24 h in feces while minimal in blood after 30 min. Although several studies have been done with cyanidin, yet very few have been conducted for anticancer activities (Fig. 9.8).

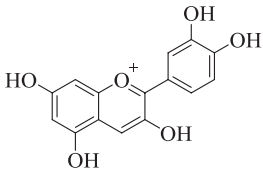
The data of various flavonoids which are clinically tested in various types of cancer patients are discussed in Table 9.2.

Fig. 9.7 Chemical structure



Genistein

Fig. 9.8 Chemical structure



Cyanidin

Table 9.2 Clinically tested flavonoids in cancer patients

Flavonoid	Patient	Study design	Intervention	Effect	References
Resveratrol	11 (colon cancer)	Phase 1	Plant-derived resveratrol tablet at a dose of 80 mg/kg and 20 mg/kg and grape powder at a dose of 120 mg/kg and 80 mg/kg	Inhibition of Wnt signaling pathway	Nguyen et al. (2009)
Epigallocatechin-3-gallate	50 (prostate cancer)	Phase 1	Dietary supplementation of defined green tea catechin extract	Favorable changes in serum prostate-specific antigen, serum insulin-like growth factor axis, and oxidative DNA damage in blood leukocytes	Nguyen et al. (2011)
Epigallocatechin-3-gallate	98 (cervical intraepithelial neoplasia)	Phase 2	Dietary supplementation of defined green tea catechin extract	Safe and acceptable for long exposure but no positive response in treated groups	Garcia et al. (2014)
Genistein	60 (bladder cancer)	Phase 2	300 mg/day and 600 mg/day oral dose of genistein for 30 days	Lower doses suppress EGFR phosphorylation	Messing et al. (2012)
Genistein	30 (healthy postmenopausal women)	Phase 1	600 mg/day genistein capsules	Safer for postmenopausal women up to 900 mg/day	Pop et al. (2008)
Cyanidine-3-glucoside	8 (healthy volunteers)	Interventional	Isotopically labeled 500 mg of cyanidine-3-glucoside	Are more bioavailable than previously perceived	Czank et al. (2013)
Resveratrol	40 (healthy volunteers)	Phase 1	0.5, 1.0, 2.5, and 5.0 g daily for 29 days	Suppress insulin-like growth factor and insulin-like growth factor binding protein-3	Brown et al. (2010)
Lycopene	18 (prostatic intraepithelial neoplasia)	Phase 1	Tomato extract containing 30 mg/day lycopene	No any difference between treatment and placebo groups was seen	Gann et al. (2015)
Silibin	12 (prostate cancer)	Phase 2	13 g/daily in three divided doses	Low half-life of silibin in blood, silibin lacks tissue penetration	Flaig et al. (2010)

4 Conclusion

So far, tremendous information has been gathered by various studies exploring the role of flavonoids as potential anticancer agents in laboratories. The prosperous findings of cell lines and preclinical studies compelled the clinicians to further take up the flavonoids in clinical trials. In human trials, the flavonoids have demonstrated prosperous results. In addition, their supplementation reduced chemotherapy- and radiotherapy-induced complications in cancer patients. However, most of these trials are single centric and enrolled relatively small number of patients. The validity of flavonoids as potential anticancer agents is yet to be proven in multicentric trials involving large number of patients. In conclusion, the outcome of clinical studies is promising and presents flavonoids as potential anticancer agents.

Conflict of Interest The authors state no conflict of interest.

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