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Phytochemicals for the Management of Melanoma

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Abstract

Melanoma claims approximately 80% of skin cancer-related deaths. Its life-threatening nature is primarily due to a propensity to metastasize. The prognosis for melanoma patients with distal metastasis is bleak, with median survival of six months even with the latest available treatments. The most commonly mutated oncogenes in melanoma are BRAF and NRAS accounting approximately 60% and 20% of cases, respectively. In malignant melanoma, accumulating evidence suggests that multiple signaling pathways are constitutively activated and play an important role in cell proliferation, cell survival, epithelial to mesenchymal transition, metastasis and resistance to therapeutic regimens. Phytochemicals are gaining considerable attention because of their low toxicity, low cost, and public acceptance as dietary supplements. Cell culture and animals studies have elucidated several cellular and molecular mechanisms by which phytochemicals act in the prevention and treatment of metastatic melanoma. Several promising phytochemicals, such as, fisetin, epigallocatechin-3-gallate, resveratrol, curcumin, proanthocyanidins, silymarin, apigenin, capsaicin, genistein, indole-3-carbinol, and luteolin are gaining considerable attention and found in a variety of fresh fruits, vegetables, roots, and herbs. In this review, we will discuss the preventive potential, therapeutic effects, bioavailability and structure activity relationship of these selected phytochemicals for the management of melanoma.

Keywords

Apoptosis; Cell proliferation; Invasion; Metastasis; Melanoma; Phytochemicals; Signaling pathways

1. INTRODUCTION

Skin cancer is the most common malignancy worldwide with particularly high incidence among fair-skinned populations [1]. Skin cancer poses a major threat to public health as incidence and mortality rates of skin cancers are dramatically increasing [2–4]. Skin cancers

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CONFLICTS OF INTEREST

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are divided into two major groups according to cellular origin as either melanoma (melanocytic) or non-melanoma (epithelial) skin cancers (NMSCs) [5]. The NMSCs are comprised of basal cell carcinomas (BCCs) and squamous cell carcinomas (SSCs) and accounts for 80 and 16 percent of all skin cancer cases respectively. Although both BCCs and SCCs arise from the epidermal basal layer, they have different characteristics [5]. Though BCCs exhibit slow growth and rarely metastasize, their SCCs counterparts metastasize 2 to 5 of the time and carry a poor prognosis if metastasis has occurred [6]. Melanoma, which accounts for only 4 percent of all skin cancers, is a potentially life-threatening skin cancer due to its propensity to metastasize. It claims approximately 80 percent of skin cancer related deaths. The prognosis for melanoma patients with distal metastasis is minimal, with median survival of only six months [7, 8]. Moreover, the incidence of melanoma is rapidly increasing worldwide. The majority of melanoma cancers occur in developed countries such as Europe, Australia, New Zealand and the United States [8, 9]. The World Health Organization reports the annual incidence of melanoma to be approximately 160,000 with an associated 48,000 deaths worldwide each year [10–12]. In recent years, melanoma is the only common cancer with an increasing incidence and death rate. More importantly, the incidence of melanoma in children is also increasing rapidly. Reports estimate that 1 in 50 Americans will be diagnosed with melanoma during their lifetime. According to an estimate from the American Cancer Society, one person dies every hour from melanoma [13, 14]. Furthermore, about 9,940 melanoma-related deaths are projected to occur in the United States in 2015 [15, 16]. A gender-based analysis predicted that approximately 42,670 men and 31,200 women are expected to be diagnosed with melanoma and about 6,640 men and 3,300 women will die from melanoma in the United States in 2015.

Melanoma develops when melanocytes proliferate abnormally and become unresponsive to the regulatory signals from fibroblasts and keratinocytes. The signaling pathways that regulate melanocyte proliferation become aberrantly activated, and thus these cells divide to develop melanoma [17–20]. Melanoma development is characterized by two distinct growth phases. The radial growth phase (RGP) is characterized by the growth of single cells or small clusters of cells confined to the epidermis and extend to the papillary dermis. Alternatively, the invasion of melanoma cells into the dermis and development of tumor-like-nodules or plaques is referred to as vertical growth phase (VGP) [17, 18, 21, 22]. Depending upon the frequency and location, melanoma of the skin can be divided into various types according to clinical and histological growth patterns. However, they all pose the same risk according to their tumor depth, mitotic index (dividing melanoma cells), ulceration and, more importantly, level of spread in the regional lymph nodes [23–25].

Depending upon the clinical and pathological growth patterns melanoma can be divided into four major subtypes [26, 27]. Superficial spreading melanoma is the most common type that accounts for approximately half to three-quarters of all diagnosed melanoma and is most common in fair skinned persons of all ages. Superficial spreading melanoma usually derived from a preexisting benign melanocytic nevus and remain confined to the epidermis (RGP) for an extended time before beginning to VGP [28]. Areas of the skin with the highest nevus density (most commonly found on the back and trunk in men and on the back and legs in women) and with intermittent sun exposure are at high risk for superficial spreading

melanoma. Nodular melanoma is the second most common type that accounts for approximately 15 to 35% of all diagnosed melanomas and is notoriously rapidly-growing and invasive. It usually develops as uniform dark blue-black, blue-red or sometimes colorless bump at the trunk, head and neck areas [29, 30]. Lentigo malignant melanoma is less common subtype of melanoma that accounts approximately 5 to 15% of cases. It occurs on sun-exposed skin of faces of middle aged to elderly adults with a history of photodamage. Lentigo maligna melanoma is slow growing and has a prolonged RGP and is less invasive [31, 32]. Acral lentiginous melanoma is the least common form that accounts for approximately 5 to 10% of all diagnosed melanomas. It develops most commonly in dark-skinned individuals such as in people of Japanese, African American, Latin American, and Native American descents [33]. The most common sites for occurrence of acryl lentiginous melanoma are the soles of the feet, palms and beneath the nail plates [34, 35]. Acryl lentiginous melanomas appear clinically as tan to brown-black, macules and patches with irregular borders and an average size of 3 centimeters [36]. Melanoma can develop anywhere in the body, including the internal organs. Some less common types of melanoma include ocular and mucosal melanoma. Ocular melanoma, which represents 3–5% of all melanoma cases, occurs inside the eyes when melanocytes of the iris or choroid layer begin to proliferate abnormally. Uveal melanoma is the most common form of ocular melanoma and primarily affects light-skinned populations [37]. Mucosal melanoma represents less than 2% of all cases of melanoma and can develop in the nose, mouth, throat, and in the genital areas [38]. This review begins with a review of the gene mutations and dysregulated signaling pathways in melanoma. Beyond this, we explain the preventative and therapeutic effects of key phytochemicals for the management of melanoma in the context of their bioavailability and structure-activity relationship.

2. GENE MUTATIONS AND SIGNALING PATHWAYS ACTIVATED IN MELANOMA

The use of advanced technology in the analysis of the human genome has helped to shed light on specific gene mutations that occur frequently in melanomas and the impact of these mutations on the regulation of signaling pathways. More importantly, studies have confirmed that these mutations control the progression and malignancy of melanomas. Some of the most frequently mutated genes found in in melanoma are described below.

2.1. BRAF Mutations

BRAF, a serine/threonine protein kinase of RAF family (ARAF, BRAF and CRAF), is generally expressed in neuronal tissues and melanocytes [39–41]. It is encoded on chromosome 7q34 and is a component of the mitogen-activated protein kinase (MAPK) pathway. MAPK a pro-growth signaling pathway is activated by cell surface growth factors receptors [42]. BRAF signaling is mutated in approximately 60% of melanomas resulting in induction of genomic instability, driving the proliferation of melanoma cells. The Sanger Institute first described activating mutations in BRAF signaling in 2002 [43]. The most common BRAF mutation (> 90% of known BRAF mutations) results from substitution of glutamic acid (E) in place of valine (V) at codon 600 (a single nucleotide mutation resulting in $BRAF^{V600E}$, nucleotide 1799 T>A; codon GTG>GAG). Mutated $BRAF^{V600E}$ leads to

hyper-activation of MAPK signaling. Another common BRAF mutation ($BRAF^{V600K}$) is the substitution of lysine (K) for valine (V) at position 600, which has been reported more common in some populations [44]. Activating mutation $BRAF^{V600E}$ has been implicated in melanoma progression by activating the downstream MEK/ERK signaling pathway and thus enhancing replicative potential, reducing senescence and apoptosis, and promoting angiogenesis [45, 46]. Activation of this pathway also stimulates cell invasion and metastasis by upregulating proteins involved in migration, cell contractility, as well as evasion of the immune response [47, 48].

2.2. NRAS Mutations

NRAS, another crucial signaling molecule of RAS family (HRAS, KRAS and NRAS), is located upstream of the BRAF/MEK/ERK (MAPK) and PI3K/AKT pathways [49–51]. After BRAF, NRAS is the second most commonly activated oncogene found mutated in 15–25% of all melanomas. Although KRAS mutations are the most common among all human malignancies, NRAS mutations are most frequently found in melanoma [52]. The substitution of an arginine (R) for a glutamine (Q) at position 61 within the NRAS protein is $NRAS^{Q61R}$. The NRAS protein is a small GTP binding proteins (guanosine-5-triphosphate; GTPase) that cleaves bound GTP and thus regulates cellular responses to many extracellular stimuli, including soluble growth factors [49]. Signal transduction through this pathway begins when extracellular growth factors interact with cell surface receptors [53]. This creates intracellular docking sites that then interact with specific adaptor molecules and signal transducing proteins leading to activation of guanine nucleotide-exchange factors (GNEFs). GNEFs remove guanine nucleotides from NRAS and allow passive binding to GTP, which is abundantly present in the cytosol. GTP bound NRAS then interacts with downstream effector molecules including BRAF, PI3K and others to regulate proliferation, survival and differentiation. Although NRAS mutations are distinct from BRAF, they both cause the constitutive activation of MAPK and PI3K/AKT signaling pathways [54, 55]. Melanomas with NRAS mutations develop higher-grade tumors with higher mitotic and invasive potentials than the BRAF mutated melanomas [56, 57]. BRAF and NRAS mutations can be detected at early stages of melanoma progression and remains activated throughout the progression of disease [58, 59]. It is well established that these mutations are almost never simultaneously present and, alone, are insufficient to initiate melanoma development [60].

2.3. PTEN Mutations

PTEN (phosphatase and tensin homologue), a tumor suppressor gene located at 10q23–24, is mutated in 30–50% of melanoma cell lines and in 5–20% primary melanomas [61–63]. PTEN functions as a dual specificity phosphatase with the ability to dephosphorylate both proteins and lipids. It can dephosphorylate phosphoserine and phosphotyrosine residues in proteins, and convert the lipid phosphatidylinositol 3,4,5-trisphosphate (PIP3) to phosphatidylinositol 4,5-biphosphate (PIP2) via dephosphorylation. As a protein phosphatase, PTEN suppress MAPK signaling through dephosphorylation of focal adhesion kinase (FAK), and regulates cell-to-cell adhesion and thus inhibits cell survival, proliferation, migration and invasion [64–66]. PTEN's lipid phosphatase activity is considered as its primary and major function. PTEN converts PIP3 to PIP2 and thus

negatively regulates the PI3K/AKT signaling pathway that is important for cell proliferation, survival, and apoptosis [67–69].

2.4. p53 Mutations

The tumor suppressor, p53, is regarded as the guardian of the genome. It responds to variety of stress stimuli, including DNA damage and hypoxia [70, 71]. p53 acts as a transcription factor for a variety of genes related to DNA repair, cell cycle progression, apoptosis and the maintenance of cellular homeostasis [72]. Mutations in the p53 gene are associated with more aggressive phenotypes in various human cancers. p53 gene mutation analysis in melanoma established that approximately 10% of all melanomas harbor p53 mutations [73, 74]. Most of these mutations are ultraviolet radiation-induced mutations [75–77]. Furthermore, higher frequency of p53 inactivation in wild type BRAF and NRAS melanoma exhibited low ERK activity, suggesting MAPK independent melanoma progression [78, 79]. Although the frequency of p53 mutations in melanomas is low, various studies have demonstrated p53's major role in the suppression of progression from nevus to melanoma [80, 81]. Several studies of superficial spreading melanoma have also found a longer relapse-free-survival rate among patients whose tumors expressed wild type p53 [82, 83].

2.5. CDKN2A/p16 Mutations

CDKN2A/p16 (also known as CDK4I or INK4a), a tumor suppressor gene associated with red hair and freckles, encodes a cyclin-dependent kinase (CDK) inhibitor p16. CDKN2A/p16 is responsible for cell cycle arrest at G1 checkpoint prior to the DNA synthesis (S) phase [84–86]. The CDKN2A/p16 protein inhibits phosphorylation and activation of retinoblastoma (Rb) proteins by CDK4 and CDK6. Since non-functional or inactivated CDKN2A/p16 shows reduced binding with CDK4, phosphorylation and activation of Rb occurs, resulting in abnormal cell proliferation [87, 88]. Cytogenetic, linkage and molecular analyses of the 9p21 region in familial and sporadic melanoma with multiple primary lesions has implicated CDKN2A/p16 as melanoma susceptibility gene [89]. CDKN2A/p16 mutations have been detected in variety of tumors including melanomas, providing evidence for CDKN2A/p16 involvement in the development of these malignancies [90, 91]. A study of 60 melanoma cell lines demonstrated that 92% of melanoma cell lines had aberrantly activated CDKN2A/p16 or CDK4. In the same study, 80% cell lines carried either non-function p16 or absent in p16 [92]. More importantly, the presence of CDKN2A/p16 germline mutations are not only associated with melanoma but also increase the risk of other malignancies such as pancreatic and breast cancer [54]. According to an estimate 5–10% of melanomas are known to be hereditary, and among those only 20–40% are associated with a pathogenic mutation in CDKN2A/p16 [93]. Frequency of CDKN2A/p16 mutation in familial melanoma ranged from 8–50% established after screening of 230 melanoma families worldwide for germline mutation in CDKN2A/p16 [94]. Furthermore, Americans who carry a CDKN2A/p16 mutation have an estimated 76% lifetime risk of developing melanoma [95]. Due to the exceptionally high probability of developing melanoma in the CDKN2A/p16 mutated population with poor prognosis of late-stage disease, it may be useful to institute a screening process to identify and warn CDKN2A/p16 mutation carriers of their high-risk status before the development of

melanoma [96–98]. Recent studies have implicated that CDKN2B mutation is also involved in the promotion and progression of benign melanocytic nevi to melanoma [99].

3. PHYTOCHEMICALS FOR THE PREVENTION/TREATMENT OF MELANOMA

The role of diet and nutrition in the prevention of disease has gained public attention recently. A growing body of scientific evidence has established the protective effect of dietary manipulation, especially the use of dietary supplements to protect the skin from various diseases such as cancer. Epidemiologic studies have also addressed the role of dietary factors in melanoma prevention. Since these dietary phytochemicals are safe and carry minimal toxicity, they hold promising potential as complementary therapies for the treatment of melanoma as well [100–103]. In the present review, we have explored the protective and therapeutic potential of dietary phytochemicals against cell proliferation, apoptosis, invasion and metastasis by targeting signal transduction pathways (Table 1 and Fig. 1). These phytochemicals includes fisetin, epigallocatechin-3-gallate, resveratrol, curcumin, proanthocyanidin, silymarin, apigenin, capsaicin, genistein, indole-3-carbinol, and luteolin.

3.1. Fisetin

Fisetin (3,3′,4′,7-Tetrahydroxyflavone) (Fig. 2A), a naturally occurring flavonoid, is commonly found in various fruits and vegetables such as strawberries, mangoes, kiwis, apples, grapes, persimmons, cucumbers and onions [104, 105]. Fisetin has shown to possess antioxidant, anti-inflammatory, and anti-proliferative properties against various cancers including melanoma and non-melanoma skin cancers [106–110]. Treatment of various malignant melanoma cell lines carrying different genetic characteristics (BRAF-mutant, NRAS-mutant, BRAF-NRAS wild type) with fisetin inhibited their invasion. Strengthening this finding, fisetin also decreased the invasive potential of melanoma cells in experiments using three-dimensional human skin equivalents. The anti-invasive effects of fisetin were associated with a decrease in the phosphorylation of MEK1/2 and ERK1/2 as well as inhibition of nuclear factor kappaB (NFκB) signaling pathway. Fisetin treatment also promoted mesenchymal to epithelial transition (MET) by decreasing mesenchymal marker proteins and increasing epithelial marker proteins [108]. Syed *et al.* [111, 112] observed downregulation of Wnt/β-catenin, PI3K/AKT, mTOR, and microphthalmia-associated transcription factor (MITF) signaling proteins in melanoma cell lines and in a three-dimensional human skin equivalent melanoma model. These findings show that fisetin is a phytochemical with promising anti-melanoma activities.

3.1.1. Bioavailability of Fisetin—Murine investigations have not been able to demonstrate any measurable toxicity of the phytochemical, fisetin [113, 114]. Bioavailability studies have demonstrated that fisetin was readily absorbed with detectable levels in the serum of mice [113, 115–117]. Pharmacokinetics studies involved conversion of fisetin-loaded dimyristoylphosphatidylcholine liposomal vesicles into nanocochleates by the action of Ca^{2+} ions. Analysis following intraperitoneal injection of nanocochleates showed a 141-fold higher relative bioavailability in mice [115]. In another study, liposomal encapsulation

of fisetin increased bioavailability by 47-fold and enhanced the anti-tumor potential when compared to free fisetin [116]. Furthermore, intraperitoneal administration of the fisetin nano-emulsion resulted in a 24-fold increase of relative fisetin bioavailability [113].

3.1.2. Structure Activity Relationship of Fisetin—The basic flavonoid structure is two benzene rings (A- and B-ring) linked through a central heterocyclic pyrane (also known as pyrone or C-ring). The 2-position of the pyrone ring is generally with B-ring. The presence of an oxy group at position 4, a double bond between carbon atoms 2 and 3 (C2=C3 double bond), and a hydroxyl group at position 3 (3-OH) of the C-ring determine the type of flavonoid compound. Flavonols (e.g., quercetin, myricetin, quercetagetin, fisetin) all have an oxygen group at position 4, a C2=C3 double bond, and a 3-hydroxyl (3-OH) group and are known to possess anti-cancer properties [118]. Furthermore, fisetin, has 3′ - and 4' -OH on the B-ring, and elimination of 3' -OH on the B-ring, 4',5,7 trihydroxyflavone (THF) (Fig. 2B), has been shown to reduce the anti-cancer potency of fisetin. The important structural features of flavonoids (3'- and 4' -OH on the B-ring, 3-OH on the C-ring, the C2=C3 double bond in the C-ring and the phenylchromone C6–C5–C6) promote inhibition of epidermal growth factor (EGF)-induced cell transformation [118]. In another study, the structure activity relationship of fisetin was examined using different derivatives of the flavonoid. Sagara *et al.* [119] evaluated four trihydroxyflavones (THF), lacking one hydroxyl group, and three dihydroxyflavones (DHF), lacking two hydroxyl groups. All the derivatives tested promoted nerve cell differentiation and protected nerve cells from oxidative stress induced death, although there was a significant difference in both potency and efficacy. The 3,3',4' THF (Fig. 2C) most effectively induced differentiation, accomplishing this in >80% cells. Furthermore, Akaishi *et al.* [120] recently reported that the 3',4'-dihydroxyl (Fig. 2D) group is essential for the inhibitory effect of fisetin on amyloid beta protein fibril formation.

3.2. Epigallocatechin Gallate (EGCG)

Green tea (*Camellia sinensis*) leaves contain many polyphenols such as flavanols (catechins), flavandiols, and phenolic acid. Among them, the four main catechins present in green tea leaves are (−)-epigallocatechin gallate (EGCG), (−)-epicatechin gallate (ECG), (−)-epigallocatechin (EGC) and (−)-epicatechin (EC) (Fig. 3A–D). Epidemiological studies suggested that regular consumption of green tea attenuates the risk of many cancers. Green tea polyphenols and EGCG are known to have antioxidant, anti-mutagenic, anti-inflammatory, and anti-carcinogenic activities. [121–123]. Evidence shows that EGCG is more potent than other catechins in reducing the human melanoma cell growth [124]. Most importantly, neither EGCG nor other catechins have any effect on growth of normal melanocytes [125]. EGCG inhibits growth, promotes cell cycle arrest, and induces apoptosis of melanoma cells by modulating cyclin-dependent kinase network and Bcl-2 family proteins [125, 126]. In addition, combining EGCG with interferon/vorinostat therapy enhanced its efficacy against melanoma by targeting NFκB signaling pathways. Combination of EGCG/vorinostat significantly inhibited melanoma cell proliferation and increased apoptosis through activation of cell cycle inhibitory proteins, modulation of Bcl-2 family proteins, and NFκB signaling pathway. A recent study established that treatment of melanoma cells with EGCG at physiological dose reduced melanoma growth by inhibiting NFκB activity [127]. This was correlated with decreased IL-1β secretion. In addition,

numerous investigations have demonstrated that EGCG inhibited many pro-inflammatory enzymes and cytokines such as iNOS, COX-2, MMPs, IL-6, IL-8, IL-12 and TNFα [128, 129]. EGCG-induced IL-1β suppression was mediated by downregulation of the inflammasome, decreased nuclear localization leucine-rich-repeat protein 1 (NLRP1), and reduced caspase-1 activation.

In a recent study, Singh and Katiyar [130] demonstrated the anti-invasive potential of various green tea catechins on human melanoma cell invasion. They showed that EGCG carried the greatest inhibitory effect of the green tea catechins, with lesser effects from EGC > ECG, GC and EC. EGCG was found to inhibit melanoma cell invasion by decreasing EMT through reduced COX-2 expression, PGE_2, and PGE_2 receptors in melanoma cells [130]. Overall these findings revealed signaling pathways by which EGCG may inhibit invasion of melanoma cells. Thus this non-toxic, dietary component of green tea, EGCG, possesses antioxidant, anti-inflammatory, anti-carcinogenic potential, which makes it a logical candidate molecule for melanoma prevention and therapeutics.

3.2.1. Bioavailability of EGCG—Centuries of tea consumption provide evidence of EGCG's safety in humans. Phase I clinical investigations have demonstrated that catechins and polyphenon E in doses ranging from 200 to 1200 mg were well-tolerated. Murine investigations found a broad range of bioavailability from 26.5% in mice to 1.6% in rats [131–133]. HPLC studies have revealed levels ranging from 5 to 150 ng/ml of EGCG, EC, and ECG in serum after oral tea consumption [134, 135]. Some bioavailability investigations have postulated that the low bioavailability may be because of the large size of the compounds [136]. The bioavailability of tea catechins in humans is relatively low at a range of only 0.2 to 2% [133, 137–139]. Oral administration of 1.5 mM of EGC, ECG and EGCG resulted in an average plasma concentration of 5 μM, 3.1 μM, and 1.3 μM respectively [140]. Oral consumption of 100 to 1600 mg of pure EGCG resulted in 0.26 to 6.35 μM of EGCG detectable in plasma after 2 to 3 hrs [141]. These studies show that tea catechins reach human plasma at the micromolar level (less than 1–2%) while the metabolites are present to a greater extent in human plasma after oral consumption of green tea [136, 142].

3.2.2. Structure Activity Relationship of EGCG—The catechins are the major components of green tea. These catechins contain a benzopyran skeleton with a hydroxyl or ester moiety at the 3-position and a phenyl group substituted at the 2-position. Catechins are classified by 2,3 subsituents and by the number of hydroxyl groups in the B- and D-ring [143]. In a recent study, using 10 different polyphenols demonstrated that anti-cancer potential of polyphenols such as catechin and epicatechin increases significantly if they were esterified with gallic acid to produce catechin gallate and ECG [144]. Among the 10 polyphenols, EGCG was most potent in inhibiting cell growth and inducing apoptosis. Although epicatechin has not demonstrated anti-proliferative effects, the catechin and epicatechin were found to significantly inhibit proliferation after esterification with gallic acid to form gallate and ECG. Similarly, gallic acid group of EGCG significantly enhanced catechin's anti-cancer potential. This property may be used to synthesize flavonoid derivatives to develop novel anti-cancer agents in the future [144]. Khandelwal *et al.* established that EGCG functions as an Hsp90 inhibitor [145]. They found that the prenyl-

substituted aryl ester of 3,5-dihydroxychroman-3-ol ring system act as a novel scaffold that exhibits greater Hsp90 inhibition than EGCG. The abilities of various green tea polyphenols to inhibit cell growth, RAS signaling, and activator protein-1 (AP-1) activity were compared. With the exception of epicatechin, all of the tea polyphenols showed strong inhibition of cell growth and AP-1 activity. Among these compounds, both the galloyl structure on the B-ring and the gallate moiety inhibited growth and AP-1 signaling with the galloyl structure contributing the strongest effects. Catechin epimers such as theaflavin-3,3'-digallate, inhibited the phosphorylation of p38. EGCG decreased levels of c-Jun, while theaflavin-3,3'-digallate decreased the level of fra-1. Based on the results they suggested that catechins and theaflavins inhibited AP-1 activity and the MAPK pathway through different mechanisms [146]. EGCG inhibited the chymotrypsin-like activity of the proteasome organelle both *in vitro* and *in vivo* at concentrations equivalent to that found in the serum of green tea drinkers. Atomic orbital energy analyses and HPLC demonstrated that the carbon of the polyphenol ester bond is necessary for inhibition of proteasome activity in cancer cells [147, 148]. In an effort to discover more stable polyphenol proteasome inhibitors, Landis-Piwowar *et al.* [149] synthesized several novel EGCG analogs and observed that elimination of hydroxyl groups from either the B- or D-ring decreased proteasome inhibition *in vitro*. Another group developed alkyl gallate and gallamide derivatives with strong anti-proliferative and apoptotic activity against human cancer cells by using the EGCG-derived galloyl group as a core structure [150]. Dodo *et al.* [150] the pioneers of the aforementioned technique, subsequently added a galloyl group into alkyl gallates and gallamides to synthesize various bisgallate and bisgallamide derivatives. This enhanced the anti-proliferative effects of gallamides but not alkyl gallates.

3.3. Resveratrol

It is a polyphenolic phytoalexin stilbenoid derivative of stilbene (Fig. 4A), produced naturally by a wide variety of plants such as grapes, peanuts, mulberries, cranberries, and eucalyptus. Resveratrol is known to possess cardio-protective, antioxidant, neuroprotective, immunomodulatory, anti-inflammatory, metabolism-regulating, and anti-cancer effects [151]. An accumulating body of evidence has shown that resveratrol inhibits cell growth and induces apoptosis in various melanoma cells by S-phase cell cycle arrest and down-regulation of cyclins [152, 153]. In addition, Caltagirone *et al.* [154] found that intraperitoneal administration of resveratrol delayed the tumor growth in mice. Fang *et al.* [155] recently found that resveratrol enhances the sensitivity of melanoma cells to radiation by inhibiting proliferation and inducing apoptosis. The anti-proliferative effects of resveratrol following radiation were associated with decreased expression of the proliferative molecules. Decreased expression of the anti-apoptotic molecules cFLIP, Bcl-2 and survivin correlated with the apoptotic effects of resveratrol after radiation. In a recent study, Gatouillat *et al.* [156] showed that resveratrol inhibited the growth of a doxorubicin-resistant B16 melanoma cells through inhibition of the G1/S phase transition, down-regulation of cyclin D1/cdk4, and increased expression of p53, which ultimately induced apoptosis. Furthermore, resveratrol reduced the growth of doxorubicin-resistant B16 melanoma cells in mice and prolonged survival of mice compared to untreated controls. In studies of DR5-positive melanoma cells, Ivanov *et al.* [157] found that resveratrol decreased signal transducer and activator of transcription 3 (STAT3) and NFκB activation, suppressed Bcl-xL

and cFLIP proteins, and enhanced cellular sensitivity to exogenous TRAIL. Furthermore, upregulation of the α-melanocyte-stimulating hormone (α-MSH) signal transduction pathway involving Wnt/β-catenin, c-kit, and MITF were suppressed by resveratrol [158]. These signaling pathways have well-established roles in the immortality, viability, and invasiveness of melanoma cells [159]. In addition, Lee *et al.* [160] found that resveratrol inhibited STAT3 acetylation, which is markedly increased in melanoma cells when compared to normal melanocytes. Inactivation of the estrogen receptor alpha (ERα) gene via methylation strongly correlates with poor prognosis as well as an aggressive phenotype of melanoma [159]. Resveratrol reactivates gene expression in tumors by reducing STAT3 acetylation [158]. In addition, it triggers protective autophagy by increasing signaling through the ceramide/AKT/mTOR pathway in B16 melanoma cells [161]. In a recent study, Trapp *et al.* [162] found that resveratrol stimulated isolated human umbilical vein cell (HUVEC) proliferation, however it resulted in growth inhibition of HUVECs grown with melanoma cells in three-dimensional co-culture and in three-dimensional spheroids. This selective effect of the compound on melanoma cells was associated with increased p53 expression and matrix protein thrombospondin-1. Resveratrol inhibited vascular endothelial growth factor (VEGF) production through enhanced expression of hypoxia inducible factor-1α. Furthermore, resveratrol reduced hepatic metastatic invasion of B16M melanoma cells inoculated intra-splenically by decreasing vascular adhesion molecule 1 expression in the hepatic sinusoidal endothelium. This consequently decreased B16M cell adhesion to endothelial cells through late activation of antigen 4. Resveratrol was found to inhibit the nuclear translocation and transcriptional activity of NFκBp65, an important inducer of EMT. This lead to significantly prolonged animal survival time and reduced melanoma tumor sizes *in vivo*. This was associated with inhibition of lipopolysaccharide induced tumor migration and decreased markers of EMT [159, 163]. These data support a potential use of mono or combination resveratrol therapy for the management of melanoma.

3.3.1. Bioavailability of Resveratrol—The bioavailability and pharmacological activity of resveratrol in rabbits, rats, and mice models have been reported after intravenous and oral administration [151]. Oral treatment of mice with 20 mg/kg resveratrol yielded the highest plasma concentration (2.6 ±1.0μM) after 5 min. In another study, Asensi *et al.* [164] reported that intravenous administration of resveratrol (20 mg/kg) to rabbits yielded its maximum concentration in plasma (42.8 ± 4.4 μM) 5 min after administration, but reduced rapidly to 0.9 ± 0.2 μM (0.2 mg/l) at 1 hr. More importantly, when the same quantity of resveratrol is administered orally, the maximum concentration reached in plasma (2–3 μM in mice and about 1 μM in rabbits or rats) within the first 5 min after administration followed by a decrease in its level to less than 0.1 μM at 1 hr [165–167]. Compounds such as glucuronides or sulfates are the most common resveratrol metabolites found in human plasma or urine following oral consumption [168, 169]. In another studies, administration of single dose of 0.5 g to 5 g resveratrol in 40 healthy volunteers showed that free resveratrol is rapidly absorbed with a comparatively low mean plasma concentration from 73 ng/mL (50.3 mmol/L) to 539 ng/mL (52.4 mmol/L) respectively [168–170]. After 5–6 hrs, the concentration of resveratrol metabolites [resveratrol-3-O-sulfate (with a maximum concentration of 1135–4294 ng/mL (3.7–14 mmol/L) and monoglucuronides] was 20 fold high than the free resveratrol with plasma half-life of 2.9 – 11.5 hrs.

3.3.2. Structure Activity Relationship of Resveratrol—Resveratrol has demonstrated its potential to inhibit melanoma growth by targeting various signaling pathways [153–157, 159, 171]. Murias *et al.* [172, 173] synthesized resveratrol derivatives by increasing the number of hydroxyl groups on the phenol rings of the stilbene structure and evaluated their anti-tumor potential against human cancer cell lines. The cytostatic activity exhibited by hydroxystilbenes with ortho-hydroxyl groups was three-fold higher as compared to hydroxystilbenes with other moieties. Hydroxylated resveratrol analogs exhibited COX-2 inhibition, while methoxylated resveratrol did not exhibit these effects. In addition, resveratrol derivatives such as 3',4′,3,5-tetrahydroxy-trans-stilbene (piceatannol), 3,4,4′,5-tetrahydroxy-transstilbene and 3,4,5,3′,4′,5′-hexahydroxy-trans-stilbene (Fig. 4B,C,E) demonstrated a 6,600-fold anti-radical activity above resveratrol. In another study, Lee *et al.* [174] found that the hydroxyl group at the meta position of the B-ring is crucial for MEK/ERK inhibition in the resveratrol analogue, 3,5,3′,4′,5′-pentahydroxy-trans-stilbene (Fig. 4D), which acts by inhibiting cell transformation. An accumulating body of evidence has demonstrated that increasing the number of hydroxyl groups on the ring-structure further enhances the cytotoxic and free-radical-scavenging effects of resveratrol [172–175]. Furthermore, Murias *et al.* [172, 173] reported that hexahydroxystilbene (M8) (Fig. 4E) was the most effective resveratrol analogue against various cancer cell lines including melanoma through inhibition of deoxynucleosidetriphosphate formation (dATP and dTTP) by inhibition of enzyme ribonucleotide reductase. Moreover, hexahydroxystilbene (M8) was active in inhibiting the melanoma growth in two different melanoma animal models. Wachek *et al.* [176] demonstrated that hexahydroxystilbene (M8) was effective in sensitizing malignant melanoma *in vivo* as a single compound and in combination with dacarbacine. In this study, animals that were treated with a combination of hexahydroxystilbene (M8) and decarbacine were found to be tumor free due to synergistic action of these compounds. Furthermore, hexahydroxystilbene (M8) inhibited cell migration in matrigel assays. In addition, hexahydroxystilbene (M8) inhibited melanoma tumor growth and prevented metastasis of melanoma cells to distant lymph nodes in the SCID mouse model [177–179]. Monohydroxylated resveratrol (also, piceatannol) possesses better anti-tumor activity than resveratrol itself and is a potent COX-2 inhibitor. Piceatannol has also been found to induce apoptosis of SK-MEL-28 melanoma cells by downregulating cyclins A, E and B1 (causing cell cycle arrest at the G2 phase) and by inhibiting NFκB signaling [152]. In fact, Ashikawa *et al.* [180] demonstrated that the hydroxyl groups of stilbenes are critical for suppression of NFκB activation. Studies using human melanoma cells demonstrated that 3,4,5,4′-tetramethoxystilbene (DMU-212) (Fig. 4F) exerts it anti-mitotic effect by ERK1/2 activation [181]. Moreover studies have demonstrated that methylation at key positions of the cis-resveratrol (Fig. 4G) form results in more potent methylated analogs of cis-resveratrol (cis-3,5,4′-trimethoxystilbene) (Fig. 4H) with enhanced anti-cancer properties [182].

3.4. Curcumin

Curcumin (Fig. 5A) is a hydrophobic, polyphenolic, bioactive compound extracted from the rhizome of the dietary spice turmeric (*Curcuma longa*). Turmeric, commonly found in curry powder, has been used for centuries in indigenous medicine as it possesses wide-range of anti-inflammatory, antioxidant, and anti-cancer properties [183]. The chemotherapeutic potential of curcumin is evident by its known abilities to induce apoptosis and cell adhesion

as well as inhibit angiogenesis in cancer cells. Phase I and phase II clinical trials have established its safety and therapeutic efficacy in cancer patients [184]. The compound was found to exert its anti-cancer effects by targeting AKT [185], NFκB [186], AP-1 [187], and c-Jun N-terminal kinase [188].

In melanoma cells, curcumin has been found to induce apoptosis through several mechanisms including upregulation of p53, p21(Cip1), p27(Kip1), and checkpoint kinase 2. It also decreases cancer cell survival by downregulating NFκB, iNOS, and DNA-dependent protein kinase catalytic subunit expression [189]. Furthermore, curcumin treatment of melanoma cells attenuated NFκB binding activity without suppressing the BRAF kinase pathway or AKT phosphorylation. Evidence suggests that curcumin decreases tumor growth by inhibiting glutathione S-transferase, inducing apoptosis through the Fas receptor/caspase-8 pathway, inhibiting COX enzymes, and by downregulating NFκB signaling [190–192]. Endoplasmic reticulum (ER) stress triggers curcumin to activate death pathways through p23 cleavage and downregulation of the anti-apoptotic Mcl-1 protein in melanoma cells [193]. Furthermore, the anti-metastatic potential of curcumin worked by downregulating collagenase activity, FAK expression, and MMP-2 function. It also modulated integrin receptors and upregulated the expression of E-cadherin [194]. Curcumin also has the potential to reverse melanoma cell multi-drug resistance by inhibiting glutathione-S-transferases [195, 196]. Elevated expression of the phosphatase of regenerating liver 3 (PRL-3), a member of tyrosine phosphatase family, has been found in highly metastatic melanomas. PRL-3, an oncogene that promotes tumor cell motility and invasion [197, 198], was downregulated by curcumin [199], thus raising its profile as a possible anti-cancer agent.

Curcumin suppresses osteopontin (OPN)-induced IκBα phosphorylation and degradation by inhibiting the IKK activity in B16F10 murine melanoma cells. Furthermore, curcumin inhibited the OPN-induced translocation of NFκBp65, NFκB-DNA binding, and NFκB transcriptional activity along with reduction of MMP activities. As a consequence of reduction in the NFκB signaling pathway, it synergistically induced apoptosis by inhibiting OPN-induced cell proliferation, migration and invasion. More importantly, curcumin suppressed the OPN-induced tumor growth in nude mice [200, 201]. Oral administration of curcumin in melanoma-tumor-bearing mice has been found to inhibit the lung metastasis of melanoma by as much as 80%, thus lengthening the survival of mice by 144% [202, 203].

3.4.1. Bioavailability of Curcumin—Pharmacological studies have shown that curcumin is non-toxic and effective in the treatment and prevention of many diseases. Epidemiological and scientific evidence have shown its beneficial health effects as antioxidant, anti-inflammatory and anti-cancer agent [204]. In one study, oral administration of curcumin 2g/kg in experimental rats resulted in 1.35±0.23 μg/ml peak serum concentration after 0.83 hr, though the same dose in humans resulted in very low serum levels (0.006±0.005 μg/ml) after 1 hr [205]. In another study, Cheng *et al.* [206] reported that 4–8 g/kg oral administration of curcumin to humans resulted in 0.41–1.75μM/ml peak plasma concentration after 1 hr. Clinical trials demonstrated a 11.1 nmol/L plasma concentration in participants one hour after 3.6 g/kg oral administration of curcumin [207]. However,

intravenous administration of curcumin in rats showed a 50-fold higher serum concentration when compared to oral administration [208].

3.4.2. Structure Activity Relationship of Curcumin—Curcumin, a natural diaryl heptanoid, can be obtained from substituted aryl aldehydes and acetylacetone, which enables the synthesis of a diverse set of curcumin analogs. Numerous analogs have been synthesized and are being tested against known biological targets to improve upon the pharmacological, absorption, distribution, metabolism and secretion profile by modifying substitutions on its aromatic rings, the β-diketone moiety, and the two flanking double bonds that are conjugated to the β-diketone moiety. This has led the way for researchers to further study the structure-activity relationship of curcumin in medicinal chemistry [209, 210]. Interestingly, Pisano *et al.* [211] recently showed that a new curcumin analog alpha,beta-unsaturated ketone D6 [(3E,3'E)-4,4'-(5,5',6,6'-tetramethoxy-[1,1'-biphenyl]-3,3'-diyl)bis(but-3-en-2-one)] (Fig. 5E) was more effective at inhibiting melanoma cell growth and inducing apoptosis *in vitro* and *in vivo* when compared to curcumin [211, 212]. Other curcumin analogs (FLLL32 and FLLL62) (Fig. 5C–D) reduced STAT3 phosphorylation resulting in apoptosis induction at micromolar concentrations in human melanoma cell lines. Furthermore, treatment with these analogs inhibited STAT3 target genes expression, uncoupled mitochondrial membrane potential and induced caspase-mediated apoptosis [213, 214]. The DM-1 compound (Sodium 4-[5-(4-hydroxy-3-methoxyphenyl)-3- oxo-penta-1,4-dienyl]-2-methoxy-phenolate) (Fig. 5B) is a curcumin analog that possesses curcumin's anti-proliferative, anti-tumor, and anti-metastatic characteristics [215]. A recent study by Zhang et al. [216] demonstrated that EF24 (diphenyl difluoroketone) (Fig. 5F) suppressed melanoma cell migration and EMT by targeting HMGA2.

3.5. Proanthocyanidins

Proanthocyanidins, the secondary metabolites of plants are present in various fruits and plant-derived beverages such as cocoa, grapes, apple, tea and red wine [183, 217, 218]. Proanthocyanidins belong to a class of condensed tannins made of (+)-catechin, (−)-epicatechin and other flavonoid oligomers and polymers. Linkages between these oligomers and polymers typically consist of B type (C4→C6 or C8) or A-type bonds (C2→O7). Grape seed extract proanthocyanidins (GSPs), the most common proanthocyanidin consumed by humans, contain B-type linkages. Grape seeds are considered as a good source of polyphenolic proanthocyanidins and procyanidins. GSPs exhibit antioxidant and anti-inflammatory properties [183, 219, 220]. GSPs are predominantly composed of proanthocyanidin, catechin or epicatechin oligomers [219]. Although GSPs have been shown to have antioxidant, photo-protective, and anti-tumor effects, their chemotherapeutic/preventive effects on melanoma are yet to be explored. In a recent study, Vaid *et al.* [221] demonstrated the effect of GSPs on melanoma cell invasion and delineated the molecular mechanism underlying these effects. GSPs inhibited melanoma cell invasion through decreased COX-2 expression and PGE_2 production. It also decreased cellular migration and phosphorylation of ERK1/2 induced by 12-O-tetradecanoylphorbol-13-acetate. GSPs also inhibited the activation of NFκBp65. Inhibition of melanoma cell invasion by GSPs increased the levels of epithelial biomarkers with a concomitant loss of mesenchymal biomarkers in melanoma cells, indicating that inhibition of invasion was related with

reversal of the EMT process [221]. In addition, a murine study found grape seed extract administration to be associated with significantly fewer metastatic pulmonary melanoma nodules (a 26% decrease) when compared to controls [222].

3.5.1. Bioavailability of Proanthocyanidins—In the United States, the average dietary intake of proanthocyanidins has been estimated to be 58 mg/day [223, 224]. Absorption of monomeric flavonoids including (+)-catechin and (−)-epicatechin following the consumption of dietary proanthocyanidins has been reported in humans and animals, either as parent compounds or conjugated metabolites. There have been limited and conflicting bioavailability studies of larger proanthocyanidins to-date [225, 226]. In a study, Deprez *et al.* [227] demonstrated that human microbiota degrade proanthocyanidins to low molecular weight phenolic compounds. Moreover, appearance of simpler compounds such as benzoic acids, phenylpropionic acids, phenylacetic acids, phenylvaleric acids, phenylpropionic acids, and phenylacetic acids in the plasma and urine have been reported after proanthocyanidin melabolism [228, 229]. Animal and human studies have demonstrated the detection of unconjugated procyanidin B2 in plasma 30 min following consumption of proanthocyanidin extracts or proanthocyanidin-rich seeds. Levels of unconjugated procyanidin B2 were found to peak approximately 2 hrs after high-dose oral proanthocyanidin administration with an associated 63% excreted in the urine within 4 days of administration [224–226]. However, the bioavailability of larger proanthocyanidins is still unclear [226, 230].

3.5.2. Structure Activity Relationship of Proanthocyanidins—Structural analogs of proanthocynidins have been synthesized and evaluated for anti-cancer potential due to their unique structures and significant biological activities. Kashiwada *et al.* [231] reported on the cytotoxic potential of proanthocyanidins in an analysis of 57 tannin-related compounds such as gallotannins, ellagitannins and condensed/complex tannins. These compounds exhibited weak cytotoxicity against RPMI-7951 human melanoma cells while being less active against several other cell lines [231, 232]. Synthesis and evaluation of anti-tumor activity of proanthocynidin was first reported by Kozikowski *et al.* [233]. Numerous compounds were synthesized and their efficacy was tested against various human cancer cell lines. Kozikowski *et al.* [234] synthesized procyanidin epicatechin oligomers and evaluated for anti-tumor potential. Cytotoxic effects were observed based on the induction of cell cycle arrest in the G0/G1 phase was associated with high degree of oligomerization and activity was observed for the epicatechin dimer, trimer and tetramer. Prodelphinidin B1, B2 and B4 showed significantly better cytotoxic activity than EGCG and prodelphinidin B3 (Fig. 6A–D). Prodelphinidin B3 and C2 were almost the same as EGCG (Fig. 6D,E) [235].

3.6. Silymarin

Silymarin, a flavanolignan extracted from the milk thistle plant (*Silybum marianum* L. Gaertn) [236, 237], possesses important therapeutic potential. Silymarin exists as a mixture of three flavonolignans, silybin, silydianin and silychristin with silybin serving as the most abundant (70–80%) and most biologically active component [238]. Pharmacological studies have shown that silymarin is safe even at higher physiological doses, which may translate to safety for human use. Silymarin possesses antioxidant, anti-inflammatory, cytoprotective,

and anti-carcinogenic properties [239, 240]. An accumulating evidence suggests that both silymarin and silybin exhibit similar chemopreventive properties [241, 242].

Silymarin has been found to inhibit migration and invasion of melanoma cells by targeting the β-catenin signaling pathway. It inhibited nuclear translocation of β-catenin, increased levels of casein kinase 1α, upregulated glycogen synthase kinase-3β (GSK-3β), enhanced β-catenin phosphorylation and thus increased binding of phosphorylated β-catenin with β-transducin repeat-containing proteins (β-TrCP) [102]. Furthermore, silymarin reduced MMP-2 and MMP-9 levels, which are down-stream effectors of β-catenin signaling pathway. In another study, Lee *et al.* [243] reported that silybin induces cell cycle arrest at G1 phase and inhibits MEK1/2, ribosomal S6 Kinase 2 signaling and phosphorylation of ERK1/2 in melanoma cells. Furthermore, it reduced NFκB, AP-1 and STAT3 activation in melanoma cells *in vitro* and *in vivo*. In addition, silymarin increased apoptosis of melanoma cells by upregulating Fas-associated proteins with death domain (FADD) expression and enhancing procaspase-8 cleavage [244].

3.6.1. Bioavailability of Silymarin—In a study Schandalik *et al.* [245] demonstrated that, after single dose of oral administration of 120 mg silybin in 14 patients demonstrated that it was quickly absorbed from the gastrointestinal tract and levels of free drug peaked within 3 hrs. Total (free + conjugated) silybin levels (≥400 ng/ml) reached a peak at about 3 to 4 hrs were >40 fold higher than the free silybin and maintained up to 24 hrs. After reaching peak concentration at about 3 to 4 hrs, free silybin levels were declined and at 12 hrs reaches to limit of quantification (2 ng/ml). Administration of single dose of silipide and silymarin (120 mg, as silybin) demonstrated a several-fold higher serum concentration of silipide after 4 hrs versus silymarin. Forty-eight hours after oral silipide and silymarin administration, 11% and 3% silybin was observed in bile, respectively [246]. This study confirmed that silybin (derived from silipide) has superior bioavalability as compared to silymarin. Furthermore, Weyhenmeyer *et al.* [247] demonstrated a linear dose-response relationship in a human investigation of oral silybin administration. Approximately 10% of total silybin in plasma was found to be unconjugated within 4–6 hrs. Moreover, elimination half-life for total silybin was ~6 hrs and about 5% of the silybin administered was excreted into the urine indicating the good renal clearance. More importantly, silymarin is very well tolerated in humans without any adverse health effects [247, 248].

3.6.2. Structure Activity Relationship of Silymarin—Since silymarin is a mixture of three isomers with silybin (Fig. 7A) acting as the most active as hepato-protective agent, Ahmed *et al.* [249] synthesized different analogous and evaluated them for structure activity relationship. The most hepato-protective analog contained a hydroxymethyl group at position 2 of the dioxanes ring. In a recent study, Agarwal *et al.* [250] synthesized and characterized a series of silybin derivatives namely 2,3-dehydrosilybin (DHS), 7-O-methylsilybin (7OM), 7-Ogalloylsilybin (7OG), 7,23-disulphatesilybin (DSS), 7-O-palmitoylsilybin (7OP), and 23-O-palmitoylsilybin (23OP). In an investigation of the anti-cancer activity of these compounds, 2,3-dehydrosilybin (DHS), 7-O-methylsilybin (7OM), 7-Ogalloylsilybin (7OG) (Fig. 7B–D) exhibited improved growth inhibitory effects compared to silybin. Results from their study clearly suggest that structural modifications

can improved the anti-cancer efficacy of silybin. Furthermore, many water-soluble semi-synthetic analogs of silybin were prepared by various laboratories but increased in water solubility led to decrease in the activity.

3.7. Apigenin

Apigenin (4',5,7-trihydroxyflavone) (Fig. 8A), a flavonoid belonging to the flavone structural class, is found in plants such as parsley, celery, artichokes and chamomile. A growing body of evidence has shown that apigenin possess antioxidant, anti-mutagenic, anti-carcinogenic, anti-inflammatory, and anti-proliferative properties [251]. In addition, preparations from chamomile have been historically used to treat cutaneous inflammation and other dermatological diseases [251]. Apigenin has been identified as a cancer chemopreventive agent owing to its potent antioxidant, anti-melanoma and anti-inflammatory activities with low toxicities [252, 253]. In two separate studies, Caltagirone *et al.* [154] and Piantelli *et al.* [254] found that apigenin inhibited melanoma tumor growth (B16-BL6 melanoma cells) *in vivo* and inhibited VEGF secretion by downregulating ERK1/2 and PI3K/AKT signaling *in vitro* [252]. Moreover, apigenin significantly decreased the invasion of melanoma cells *in vitro* and inhibited lung metastasis *in vivo* by reducing lung colonization of B16-BL6 cells in mice [154, 254]. In a recent study, Das *et al.* [255] observed that apigenin inhibits cell growth and induced apoptosis in A375 melanoma cells with no concomitant toxicity to peripheral blood mononuclear cells. Further, apigenin's therapeutic efficacy was enhanced by the poly-lactic-co-glycolide formulation, since this vehicle readily enters cancer cells, intercalates with dsDNA, and induces conformational change [256].

3.7.1. Bioavailability of Apigenin—Apigenin's low intrinsic toxicity and anti-cancer potential have gained attention in recent years. The pure form of apigenin is unstable and least soluble in water and organic solvents. In nature, apigenin exists in the form of water-soluble glycoside conjugates and acylated derivatives [257, 258]. The absorption and bioavailability of apigenin is determined by conjugated moiety, since the compound undergoes enzymatic cleavage by mammalian or microbial glucosidases before absorption. It has been found that apigenin remains bound to β-galactoside in its natural form, which provides its best bioavailability [259–261]. In the gut, apigenin is metabolized via uridine 5'-diphospho-glucuronosyltransferase UGT1A1 as glucoroside and sulfate conjugates, which are more easily excreted in bile or urine. Gradolatto *et al.* [259] have shown that apigenin appeared in the blood 24 hrs after oral intake of a single dose of radio labeled apigenin. In rats, oral intake after a single dose of radio-labeled apigenin resulted in 51% detection of 51, 12, 1.2, 0.4, 9.4, 1.2, and 25% of the radioactive compound in urine, feces, blood, kidneys, intestine, liver, and the remaining tissues, respectively, within 10 days. Furthermore, kinetics of apigenin in blood exhibited a relatively high elimination half-life of 91.8 hrs (slow excretion) compared to other dietary flavonoids [258, 261]. These results clearly demonstrated the limited bioavailability of apigenin, though slow pharmacokinetics may lead to possible accumulation of this flavonoid in the tissues to effectively impart its chemopreventive effects [259–262].

3.7.2. Structure Activity Relationship of Apigenin—Protoapigenone, a natural apigenin derivative, has demonstrated a 10-fold greater anti-tumor activity than apigenin *in vitro* and *in vivo* [143, 263, 264]. Several apigenin derivatives have been synthesized and studied for their anti-cancer potential [265, 266]. Derivatives such as 1'-O-alkyl-protoapigenone and protoapigenone 1'-O-butyl ether (Fig. 8B,C) exerted significantly stronger activity than the non-substituted analog protoapigenone. On the contrary, β-naphthoflavone derivatives containing same pharmacophore when substituted with an O-alkyl side-chain at position 1 showed decreased cytotoxic activities. Furthermore, Liu *et al.* [267] demonstrated that nitrogen-containing apigenin analogs (R= ethylamino, propylamino, isopropylamino etc.) showed better anti-cancer and antioxidant potential (Fig. 8D).

3.8. Capsaicin

Capsaicin (Fig. 9A), a pungent component of chili peppers, is one of the most commonly used spices in the world [268]. Though capsaicin has historically been used for its anti-inflammatory and analgesic abilities [268], it is receiving increasing attention for its anti-tumor properties [269]. Evidence suggests that capsaicin induces A375 melanoma cell apoptosis by activating caspases 3, 8, and 9, which is accelerated by its downregulation of Bcl-2 [270]. It also reduces melanoma cell survival by decreasing NFκB activity [271, 272]. The compound was found to inhibit growth and increase apoptosis of A375 and SK-MEL-28 melanoma cells by inhibiting plasma membrane NADH oxidase activity [273]. It also inhibited the migration of B16-F10 melanoma cells through inhibition of the PI3K/AKT/Rac-1 pathway [268]. The compound's effects on VEGF are currently under debate, however. While Patel *et al.* [271, 272] found that capsaicin decreased cell proliferation through enhanced VEGF production in A375 melanoma cells. Min and colleagues [274] observed its ability to decrease angiogenesis in cultured human endothelial cells. Despite the current uncertainty of capsaicin's effects on VEGF production, the body of evidence suggests that capsaicin promotes apoptosis, decreases survival, and inhibits migration of melanoma cells.

3.8.1. Bioavailability of Capsaicin—Capsaicin is a lipophilic compound that has demonstrated fast absorption and a short half-life in humans. In addition, the compound resists diffusion and *in vitro* studies have shown that it exhibits a slow cutaneous biotransformation in humans [275, 276]. After intragastric administration of 15 mg/kg body weight capsaicin in rats, the plasma concentrations peaked to approximately 10 ng/ml after the first hr and then declined rapidly, with an absolute bioavailability of orally administered capsaicin to be 0.106% [277, 278]. According to Chaiyasit *et al.* [279] oral administration of capsaicin (26.6 mg) in humans resulted in maximum plasma concentration of 47.1 (2.0) min with $T_{1/2}$ of 24.9 (5.0) min, and 2.5 (0.1) ng ml^{-1} of C_{max}. In another study conducted by Suresh and Srinivasan [280], oral administration of 30 mg/kg body weight capsaicin in rats demonstrated 94% bioavailability. In a recent study, Rollyson *et al.* [281] demonstrated that orally administered capsaicin resulted in detectable levels in the liver, lungs, kidney and serum of the mice within 15 min after oral administration. The maximum concentration was observed at 60 min and the lungs exhibited the greatest absorption.

3.8.2. Structure Activity Relationship of Capsaicin—The cytotoxic potential of vanilloid compounds was evaluated by modifying vanilloid ring pharmacophores and nonivamide analogs of capsaicin versus the transient receptor potential vanilloid-1 (TRPV1). Specific regions of the compound including the aromatic "A-ring", the hydrogen bond-donating group in the "B-region" and the hydrophobic hydrocarbon "C-region" tail are required for maximum potency at TRPV1 [282–285]. Analogs with "A-ring" modification such as 6-iodo-nordihydrocapsaicin (Fig. 9B) and 3-methoxy-4-hydroxybenzyl have been identified as the most potent. Removal of the 4-OH or 3-MeO moieties or modification of positions 2, 5 and 6 of the "A-ring" has been found to significantly reduce its activity [277, 286, 287].

3.9. Genistein

Genistein (4',5,7-trihydroxyisoflavone) (Fig. 10A), a phytoestrogen and isoflavone found in soybeans with structural and functional similarities to estrogen, has anti-inflammatory and antioxidant effects with ongoing investigation into its ability to prevent and treat cancer, metabolic syndrome, diabetes, and chronic inflammatory diseases. Genistein has been found to inhibit angiogenesis, promote apoptosis, reduce tumor metastasis, and decrease proliferation in various malignancies ranging from neuroblastoma to breast cancer [100, 288, 289]. It has been found, however, to promote melanoma cell differentiation through stabilization of protein-linked DNA strand breakage in SK-MEL-131 cells [290, 291]. Genistein has been shown to have beneficial effects against various melanoma cells by inhibiting cell cycle progression and inducing apoptosis while inhibiting tumor growth and metastasis potential of B164A5 melanoma cells in C57BL/6J mouse model [289, 292, 293]. Genistein inhibited cell cycle progression in melanoma cells by targeting cellular p53, p21, checkpoint kinase 2 (Chk2) [294–297]. Furthermore, it inhibited invasion, cell adhesion and lung metastasis of melanoma cells in mice [298–300]. It also inhibited angiogenesis in mouse model of melanoma [288, 301]. Moreover, it induced differentiation of mouse and human melanoma cells [302–304].

3.9.1. Bioavailability of Genistein—Genistein's high lipid solubility, significant first-pass metabolism and fast gut transit time strongly limit its bioavailability [305, 306]. However, Coldham *et al.* [307] observed a peak serum concentration 30 min after an oral administration of 4 mg/kg. In another study, Steensma *et al.* [308] were able to detect serum genistein 15 min after portal vein administration. Oral treatment yielded a 5.49 μM maximum concentration after 15 min. In another study, Kwon *et al.* [309] found that 4, 20 and 40 mg/kg genistein oral administration resulted in 39, 24 and 31% bioavailabilities, respectively. Oral genistein treatment (40 mg/kg) yielded a T_{max}, C_{max} and $AUC_{(0-\infty)}$ of 2 hrs, 4880 ng/ml and 0.03 mg hr/ml, respectively. It is suggested that in infants, consumption of 4–7 mg/kg per day of total genistein will result in 1–5 μM of total circulating genistein. Adults can safely consume 1mg/kg of genistein per day resulting in ~0.5 μM serum concentration. An accumulating body of evidence has shown that genistein is safe and very well tolerated in humans [310–312].

3.9.2. Structure Activity Relationship of Genistein—Several synthetic analogs of genistein have been developed to explore its potential beneficial effects [313]. Ullah *et al.*

[314] found that genistein possessed greater antioxidant and DNA-protective effects than its methylated structural analogue biochanin A (Fig. 10B). Genistein derivatives with substitutions at the C7 hydroxyl group of the A-ring exhibited anti-mitotic activity while analogs substituted at the 4′-position of the B-ring (Fig. 10C) induced p53-independent G1 cell-cycle arrest and autophagy [315]. In addition, genistein derivatives have been found to be non-genotoxic [316]. Several studies have shown that genistein glycoconjugates (Fig. 10D) exhibit anti-proliferative potential [313, 317, 318] and even induce cell cycle arrest [319, 320]. Interestingly, some of these analogs also inhibited microtubule assembly [318, 319, 321].

3.10. Indole-3-Carbinol

Indole-3-carbinol (I3C) (Fig. 11A) is a bioactive metabolite of glucosinolate glucobrassicin, a substance found at high concentrations in vegetables from the family *Cruciferae* including broccoli, cauliflower, and Brussels sprouts [322, 323]. The compound has been found to inhibit proliferation through various mechanisms in various cancer cell lines [322]. Animal models have also demonstrated the promise of I3C in the prevention of chemical-induced tumorigenesis of breast, liver, lung, cervical, and gastrointestinal tract tissues [324]. Thus far, I3C has only been found to promote apoptosis in melanoma cell lines. In addition, I3C sensitized G361 melanoma cells to UVB radiation through decreased anti-apoptotic Bcl-2 expression [325]. Another study found that I3C induces apoptosis in SK-MEL-5 melanoma cells by down-regulation of MITF [326]. Furthermore, I3C-mediated anti-proliferative effect was through interaction with neuronal precursor cell-expressed developmentally down regulated 4 and wild-type PTEN degradation in human melanoma cells [327]. I3C consumption was also associated with increased sensitivity to chemotherapy in a study of mice with B16 melanoma [328]. I3C is a promising compound that may be effective in melanoma therapy, especially since evidence suggests that it decreases the expression of MITF, a signaling molecule known to be over-activated in resistant cases of melanoma [326].

3.10.1 Bioavailability of Indole-3-Carbinol—Consumption of vegetables from the cruciferous family serves as a good source of the I3C precursor, glucobrassicin. Mechanical damage to cells from these plants (e.g., during chewing or chopping) results in the formation of I3C from the interaction between myrosinase and glucobrassicin [186, 323]. After oral ingestion, I3C combines with gastric HCl to form a complex mixture of biologically active compounds such as a 3,3'-diindolylmethane dimer and a cyclic trimer. However, acid condensation products are less likely to form in the more alkaline environment of the intestine. To date, there have been few animal studies investigating the bioavailability of I3C [329, 330]. A phase 1 clinical trial demonstrated undetectable plasma concentrations of I3C in women who received 400 to 1200 mg oral doses. However, DIM levels (Fig. 11B) were detectable with a Cmax of 61 ng/mL and 607 ng/mL after 400 and 1000 mg doses, respectively [329, 330].

3.10.2. Structure Activity Relationship of Indole-3-Carbinol—Due to its significant anti-cancer potential but weak acid stability, several successful attempts have been made to synthesize structural analogs of I3C such as (p-substituted phenyl)-diindoylmethanes

peroxisome proliferator-activated receptor γ agonists [331–335], SR13668 (Fig.11H) as an AKT inhibitor [336, 337], and an I3C tetrameric derivative (Fig. 11C) as a CDK6 inhibitor [338]. Acid-catalyzed condensation resistant analog OSU-A9 ([1-(4-chloro-3-nitrobenzenesulfonyl)- 1H-indol-3-yl]-methanol) (Fig. 11G) exhibited significantly improved pro-apoptotic (100-fold higher) and anti-tumor properties than I3C *in vitro* and *in vivo* [324, 339]. In addition, I3C-based N-alkoxy derivatives produced a marked increase in cell cycle arrest and apoptosis. Furthermore, the inhibitory potential of 3-methoxymethylindole and 3-ethoxymethylindole (Fig. 11D–E) was similar to I3C. The hydroxymethyl group at the C-3 position of the indole ring is likely important in I3C's ability to induce cell cycle arrest since substitutions at that position was found to inactivate the compound [340]. Another I3C analog, 1-benzyl-I3C (Fig. 11F), displayed an approximate 1000-fold stronger abilities to inhibit proliferation, induce cell cycle arrest and down-regulate the production of ERα protein in estrogen responsive cancer cells [341].

3.11. Luteolin

Luteolin (Fig. 12A) is a flavanoid found in a wide variety of dietary sources such as carrots, peppers, celery, olives, peppermint, thyme, rosemary, and oregano with known antioxidant, anti-inflammatory, and anti-tumor activities. It has been found to inhibit angiogenesis, promote apoptosis, and sensitize cells to anti-cancer therapy in a variety of malignancies [342]. The compound was found to induce melanogenesis and reduce invasive potential of B16F10 melanoma cells by decreasing EMT through inhibition of the β3 integrin/FAK signal pathway [343–345]. Luteolin protected DNA, inhibited cell cycle progression and promoted apoptosis in A375 melanoma cells in a different investigation [346–348]. In addition, the compound was found to inhibit cell growth and increase apoptosis (B16 and 4A5 melanoma cells) via Bcl-2 downregulation and Bax upregulation [349]. An *in vitro* study of B16 melanoma cells showed that the flavanoid decreased ERK1/2 signaling [350]. This compound exhibits promising preliminary activity against melanoma, though further investigation will be necessary to confirm its efficacy in the management of the disease.

3.11.1. Bioavailability of Luteolin—Shimoi *et al.* [351] observed free luteolin and its conjugates present in plasma after administration of the compound to rats and humans. Plasma concentrations of luteolin and its conjugates peaked between 15 and 30 min after treatment with luteolin. Luteolin was absorbed more rapidly when administered with propyleneglycol versus 0.5% carboxymethyl cellulose. Furthermore, Zohu *et al.* [306] reported that the absorption rate constant of pure luteolin (5.0 microg/mL) was markedly higher in the duodenum and jejunum than the colon and ileum. Luteolin was likely passively absorbed given that it was taken up in an ATP-independent manner. Furthermore, oral administration in rats resulted a peak concentration and AUC of 1.97 ± 0.15 microg/mL and 10.7 ± 2.2 microg/mL/hr, respectively [306].

3.11.2. Structure Activity Relationship of Luteolin—Though luteolin is known for its antioxidant, anti-inflammatory, and anti-tumor activities, limited studies on its structure-activity relationship have been conducted. In one study, Cheng *et al.* [352] synthesized luteolin analogs by replacing hydroxy groups at C-3' and C-4' with alkynyl groups using neutral, electron-deficient, electron-rich and heteroaromatic (4-pyridine, imidazole alkynes)

at the C-4' position. This luteolin analog LA-12 (Fig. 12B), more efficiently sensitized cells to TNFα-induced cell death than did luteolin.

4. CONCLUSIONS AND FUTURE DIRECTIONS

Melanoma, with its unique ability to metastasize early, is the most deadly skin cancer affecting humans. Patients with metastatic melanoma face a median survival time of only six months and have very few targeted chemotherapies available to them. Although personalized chemotherapies targeting common mutations such as BRAF and MEK have been developed recently, these drugs have only been found to extend progression free survival by a few months. Patients who attempt these treatments frequently develop resistance and succumb to their disease. Recent studies of combination chemotherapies for the prevention and treatment of melanoma give us hope that achieving a cure is indeed possible. If ongoing investigations continue their current trajectory, the anti-cancer properties of phytochemicals may yield complimentary chemotherapies to augment today's treatments. Accumulating evidence has recently begun to illuminate the various pathways by which these bioactive molecules promote apoptosis, inhibit proliferation and suppress EMT of melanoma cells. By targeting multiple disrupted signaling molecules critical to the pathogenesis of melanoma, phytochemicals such as fisetin, EGCG, silymarin, proanthocyanidin, resveratrol, curcumin, apigenin, capsaicin, lupeol, genistein, indole-3-carbinol and luteolin may one-day serve as necessary adjuvant chemotherapies to successfully treat metastatic melanoma with minimal toxicity. This review highlights the largely untapped anti-cancer potential that phytochemicals possess. The obvious need for effective combination therapies to combat melanoma and the therapeutic promise that phytochemicals offer grant us a glimpse at a cure for melanoma. Ongoing studies are needed to evaluate various combinations of phytochemicals with existing drugs such as BRAF and MEK inhibitors. Numerous combinations of phytochemicals and targeted chemotherapies will need to be evaluated to determine which pairings yield the greatest synergy so that translational studies may then be attempted.

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LIST OF ABBREVIATIONS

AP-1	Activator protein-1
CDKN2A	Cyclin-dependent kinase inhibitor 2A
COX	Cyclooxygenase
EMT	Epithelial-mesenchymal transition
FAK	Focal adhesion kinase
FLIP	Cellular FLICE-like inhibitory protein
GSK-3β	Glycogen synthase kinase-3β

GTP	Guanosine-5-triphosphate
MAPK	Mitogen-activated protein kinase
MITF	Microphthalmia-associated transcription factor
MMP	Matrix metallopeptidase
mTOR	Mammalian target of rapamycin
NFκB	Nuclear factor kappa B
NLRP1	Nuclear localization leucine-rich-repeat protein 1
PGE_2	Prostaglandin E_2
PI3K	Phosphatidylinositol 3-kinase
PTEN	Phosphatase and tensin homolog
Rb	Retinoblastoma
RGP	Radial growth phase
STAT3	Signal transducer and activator of transcription 3
VGP	Vertical growth phase
α-MSH	Alpha-melanocyte-stimulating hormone

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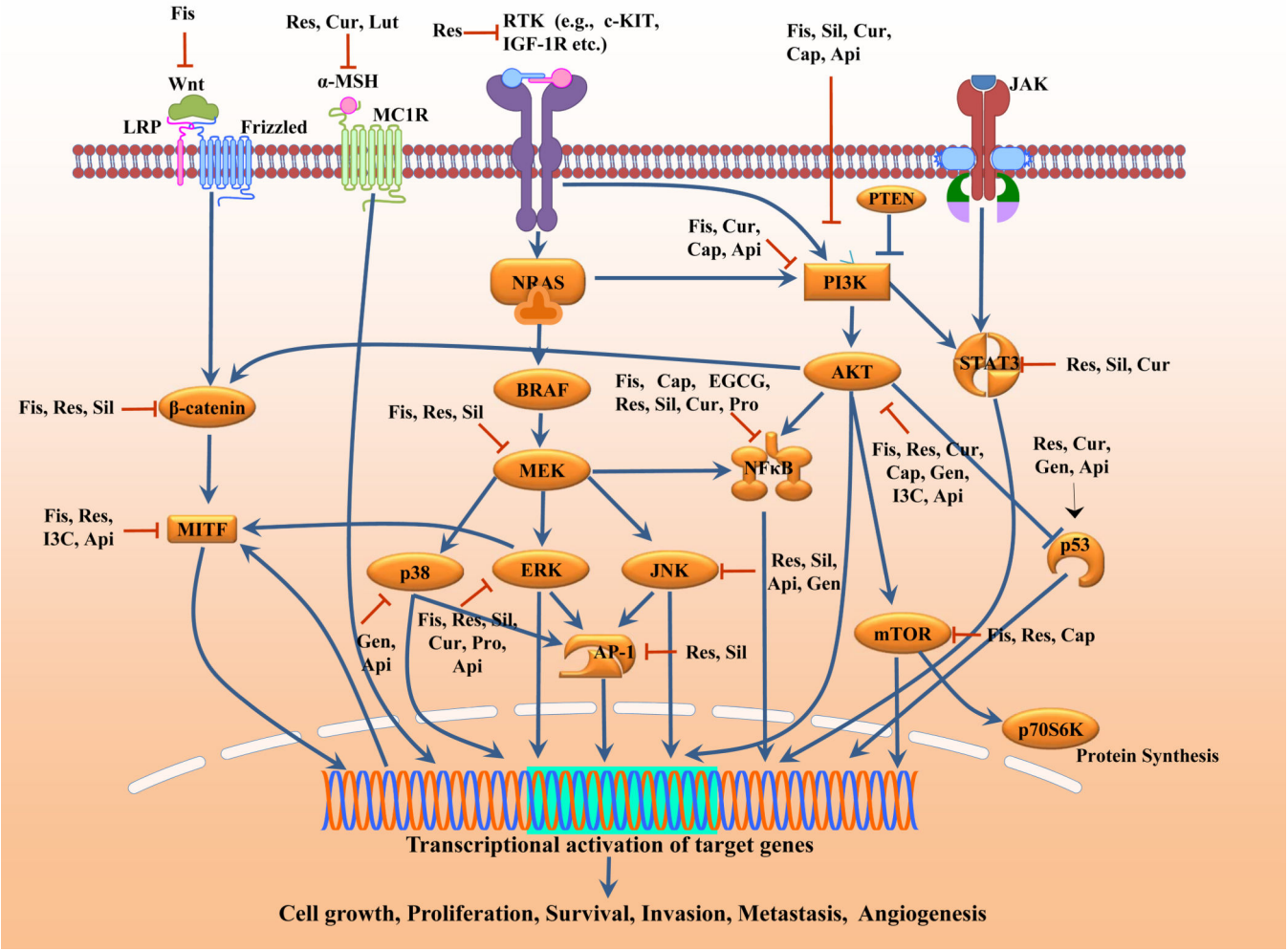


Fig. 1.

Signal transduction pathways altered by selected phytochemicals. Fis inhibits PI3K, AKT, mTOR, NFκB, MEK, ERK, Wnt, β-catenin, MITF; EGCG inhibits NFκB; Res inhibits AKT, mTOR, NFκB, MEK, ERK, β-catenin, MITF, STAT3, c-kit, c-Jun, α-MSH; Sil inhibits NFκB, MEK, ERK, β-catenin, STAT3; Cur inhibits PI3K, AKT, NFκB, ERK, STAT3; Pro inhibits NFκB, ERK; Cap inhibits PI3K, AKT, mTOR, NFκB; Gen inhibits AKT, p38; I3C inhibits AKT, MITF; Lut inhibits α-MSH; Api inhibits PI3K, AKT, ERK, MITF, p38. p53 is upregulated by Res, Cur, Gen, Api.

Abbreviations: Fis=Fisetin, EGCG=Epigallocatechin gallate, Res=Resveratrol, Sil=Silymarin, Cur=Curcumin, Pro=Proanthocyanidin, Cap=Capsaicin, Gen=Genistein, I3C=Indole-3-carbinol, Lut=Luteolin, Api=Apigenin

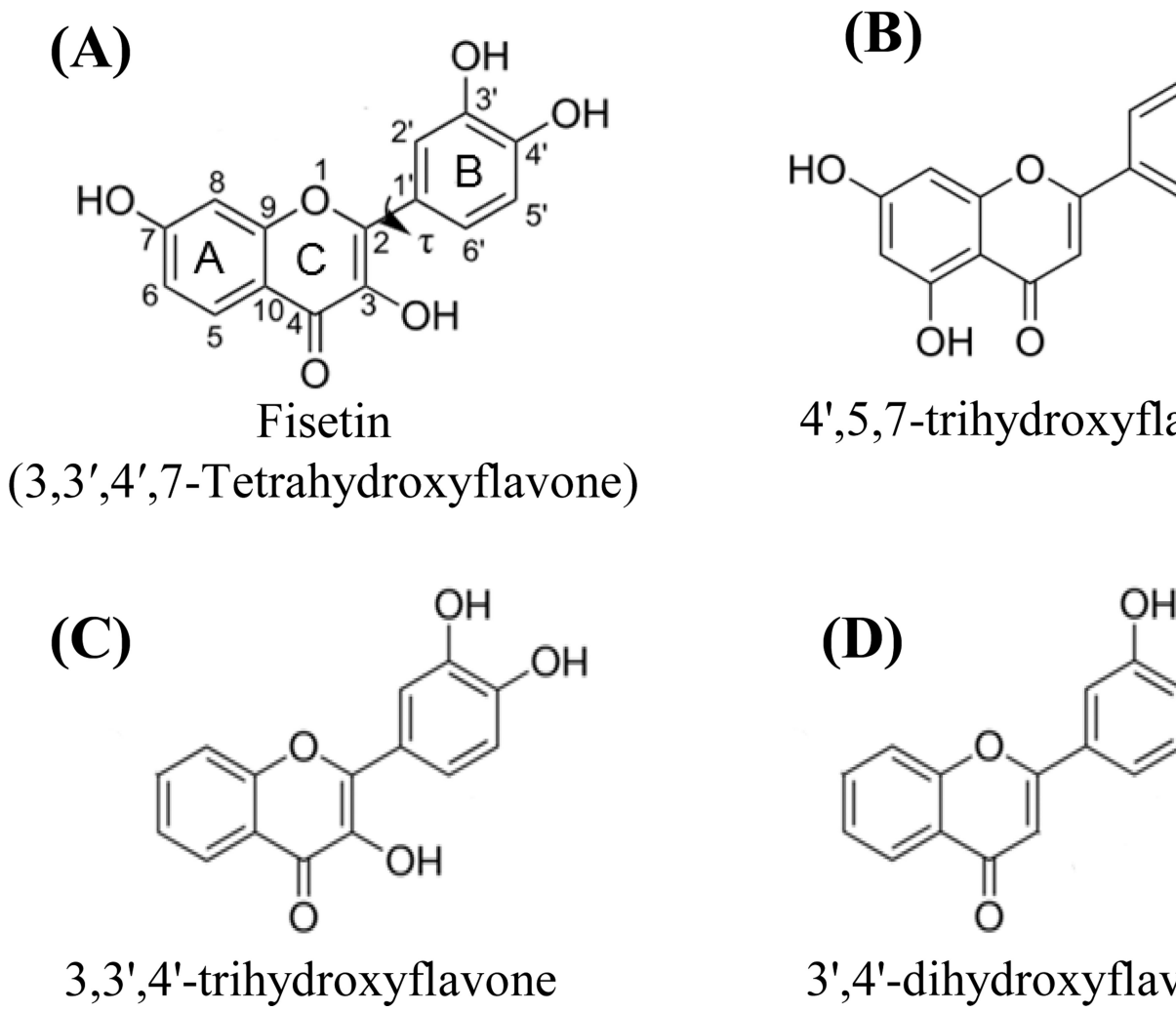
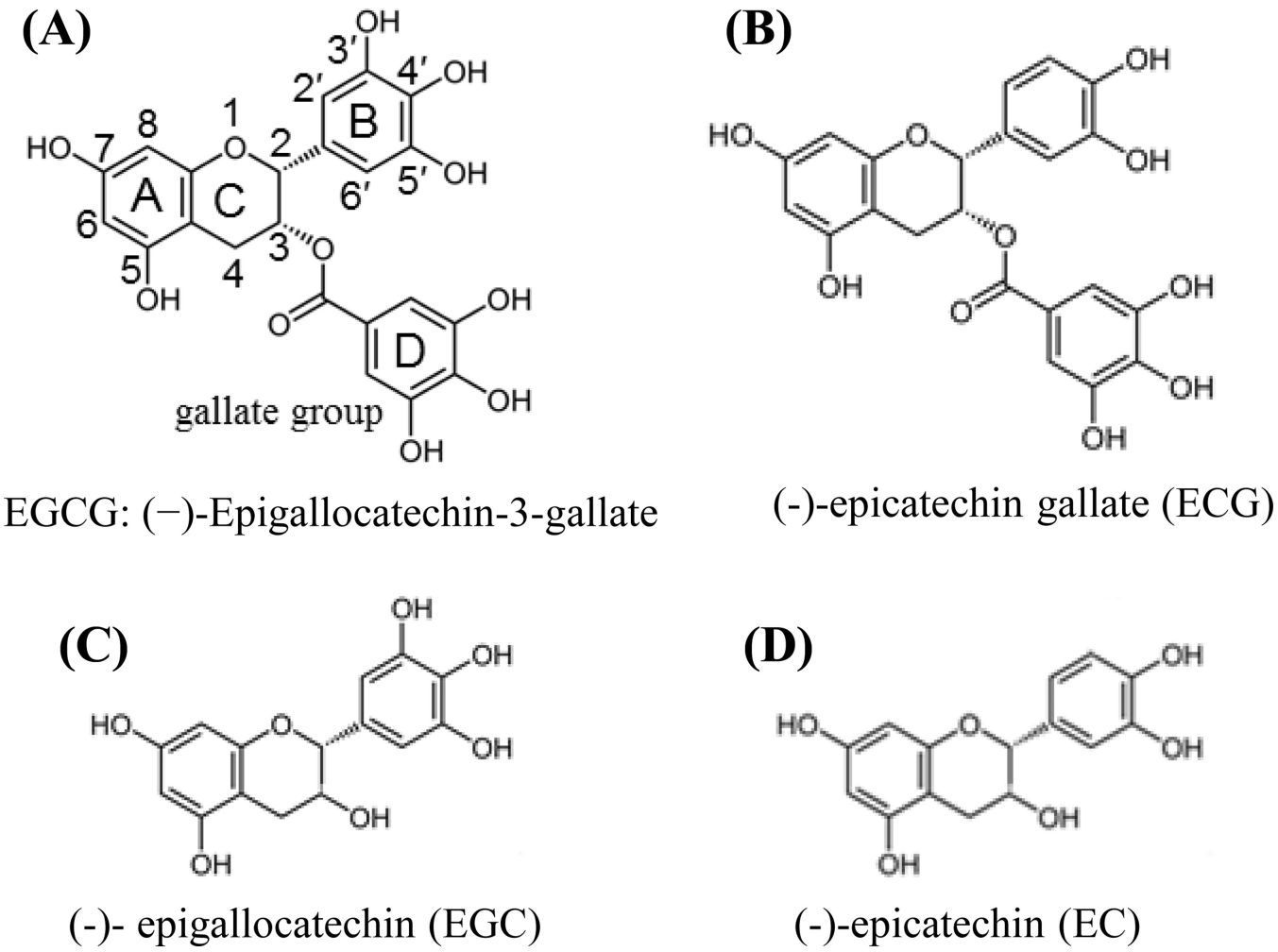


Fig. 2.
Fisetin and its structural analogs.



EGCG: (−)-Epigallocatechin-3-gallate

(-)-epicatechin gallate (ECG)

(-)- epigallocatechin (EGC)

(-)-epicatechin (EC)

Fig. 3.
EGCG and its structural analogs.

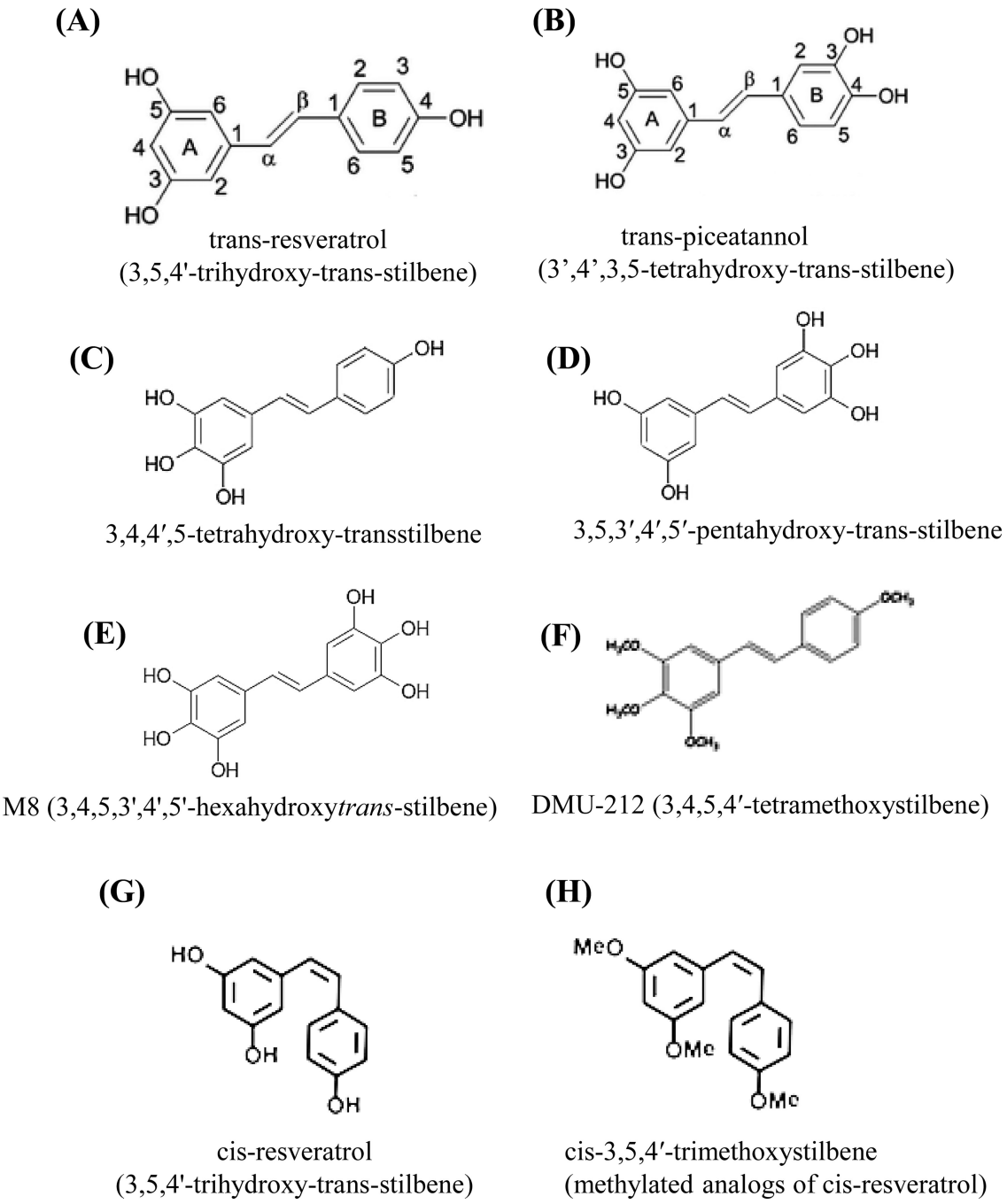


Fig. 4.
Resveratrol and its structural analogs.

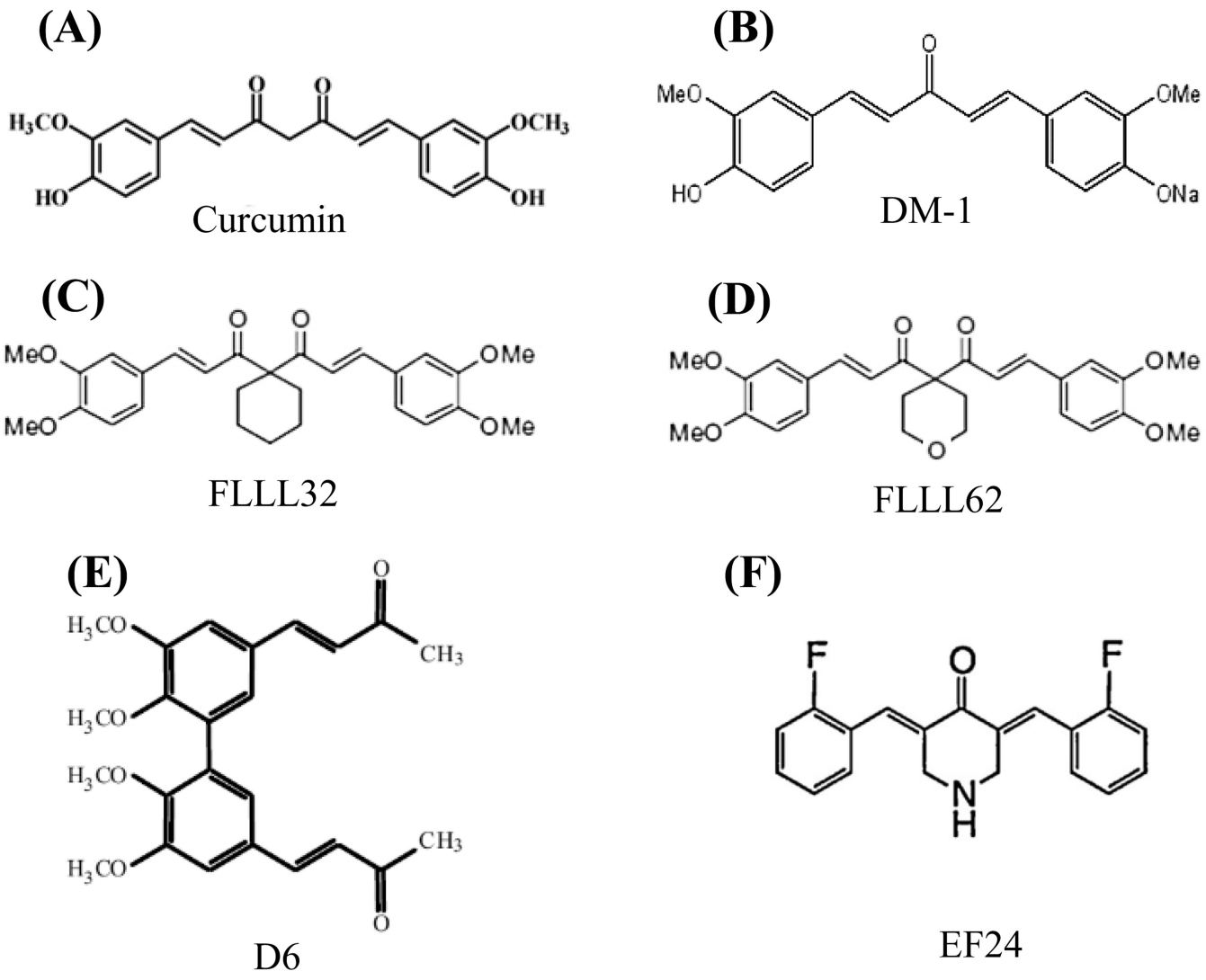


Fig. 5.
Curcumin and its structural analogs.

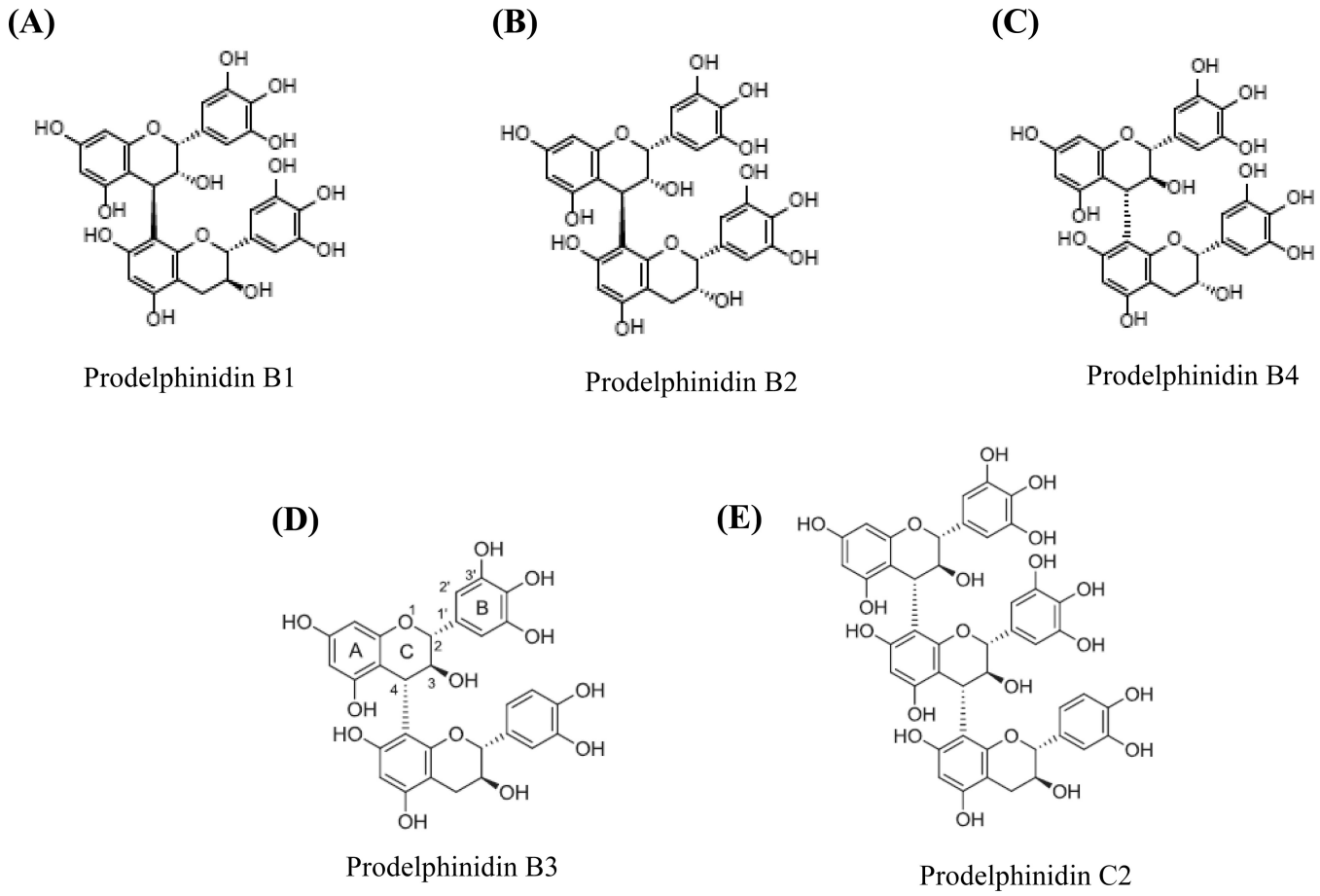


Fig. 6.
Proanthocyanidin and its structural analogs.

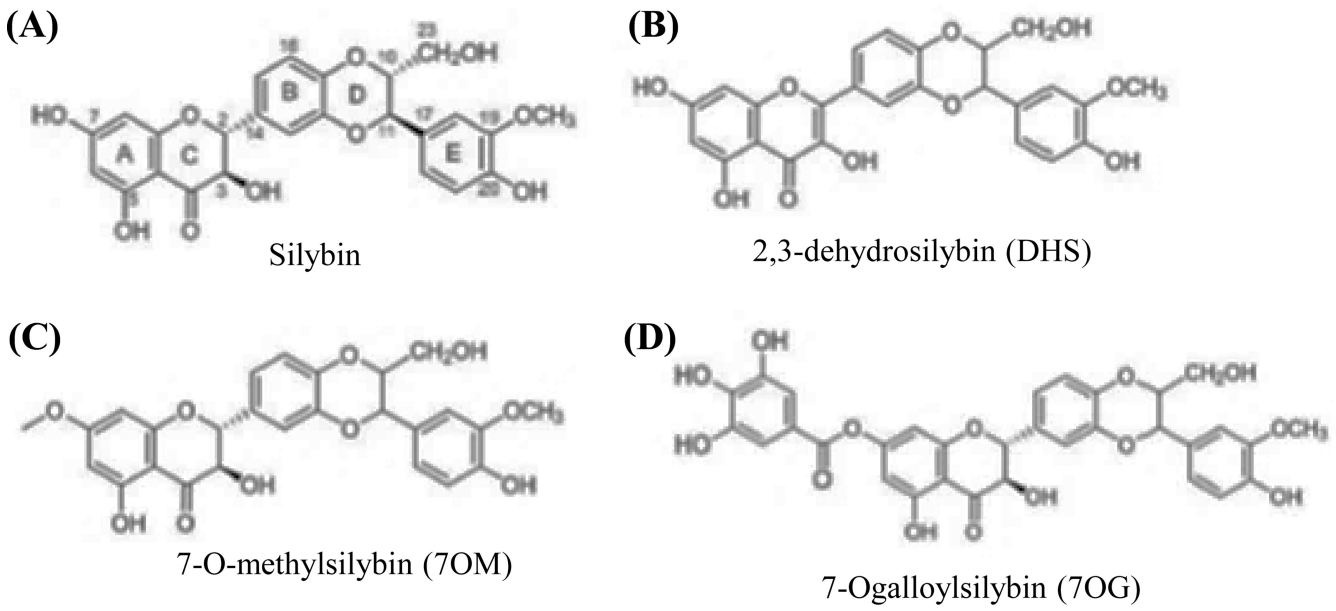


Fig. 7.
Silybin and its structural analogs.

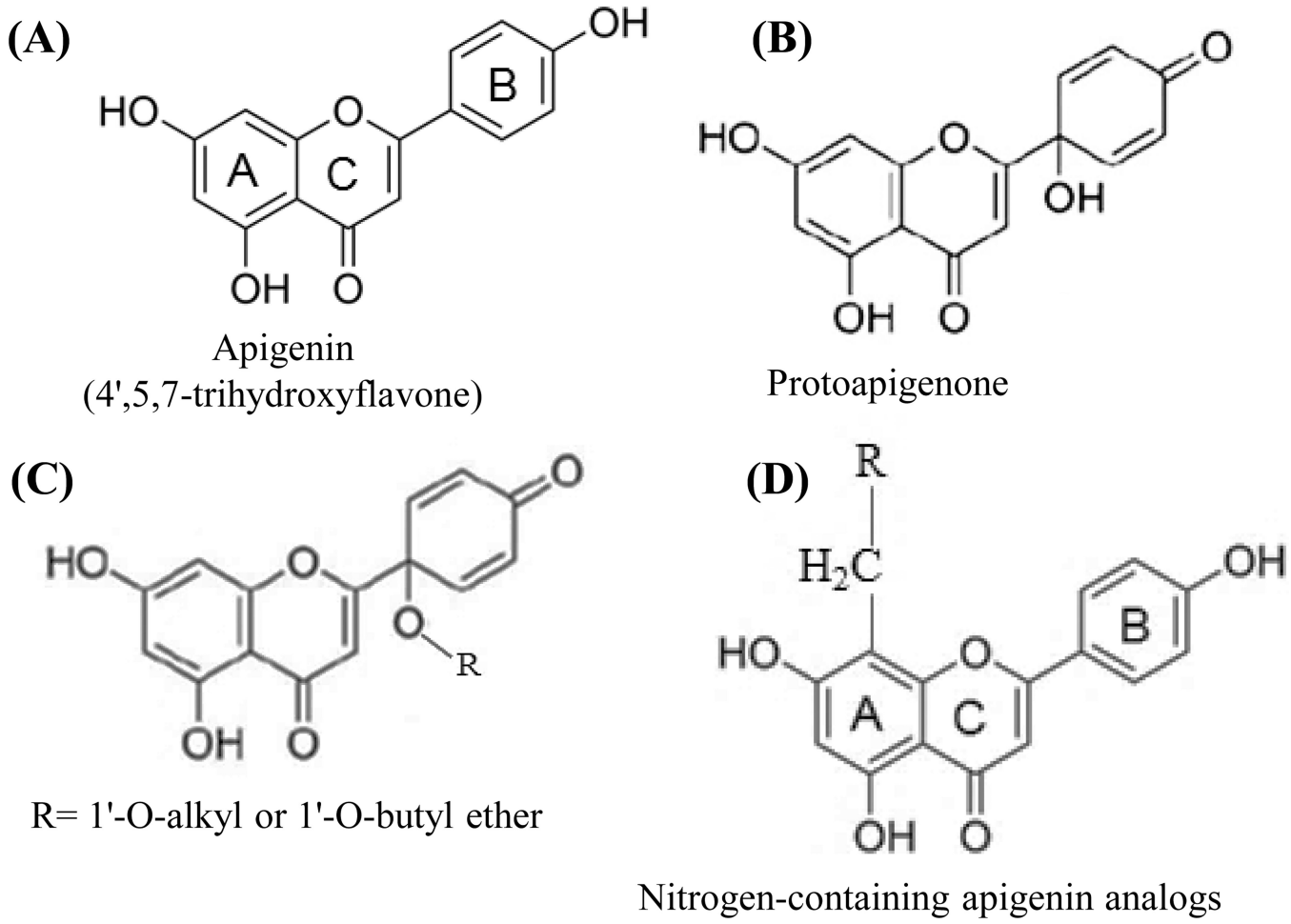


Fig. 8.
Apigenin and its structural analogs.

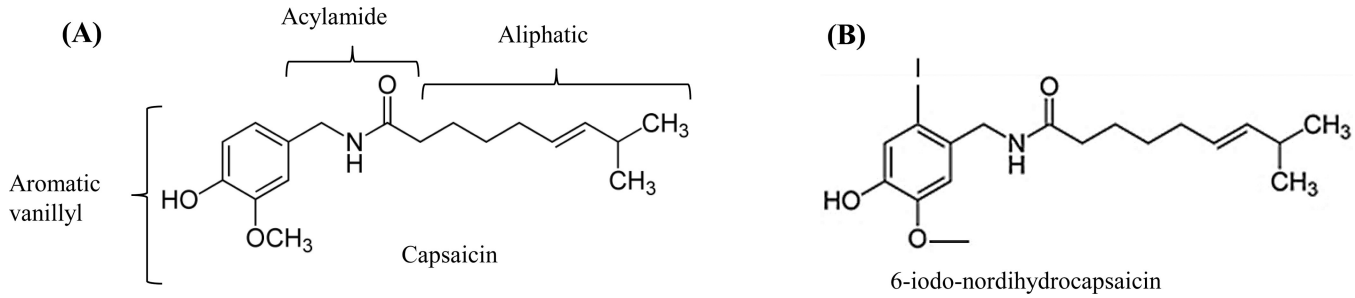


Fig. 9.
Capsaicin and its structural analogs.

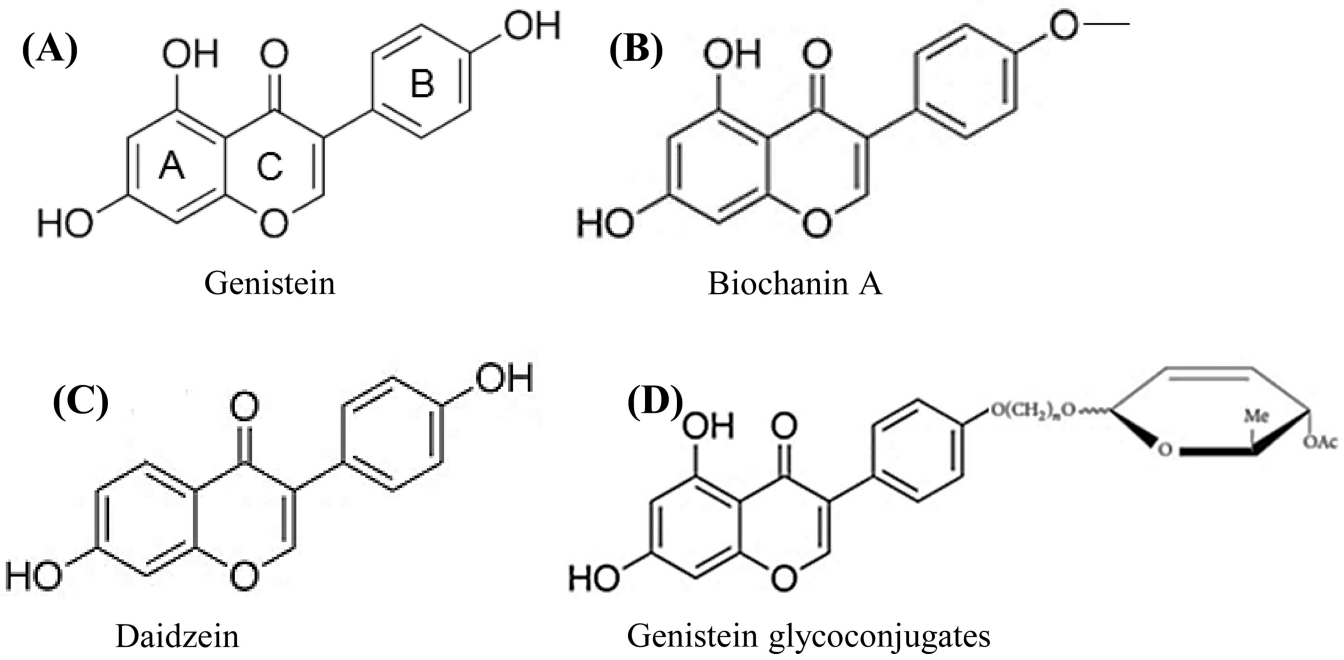


Fig. 10.
Genistein and its structural analogs.

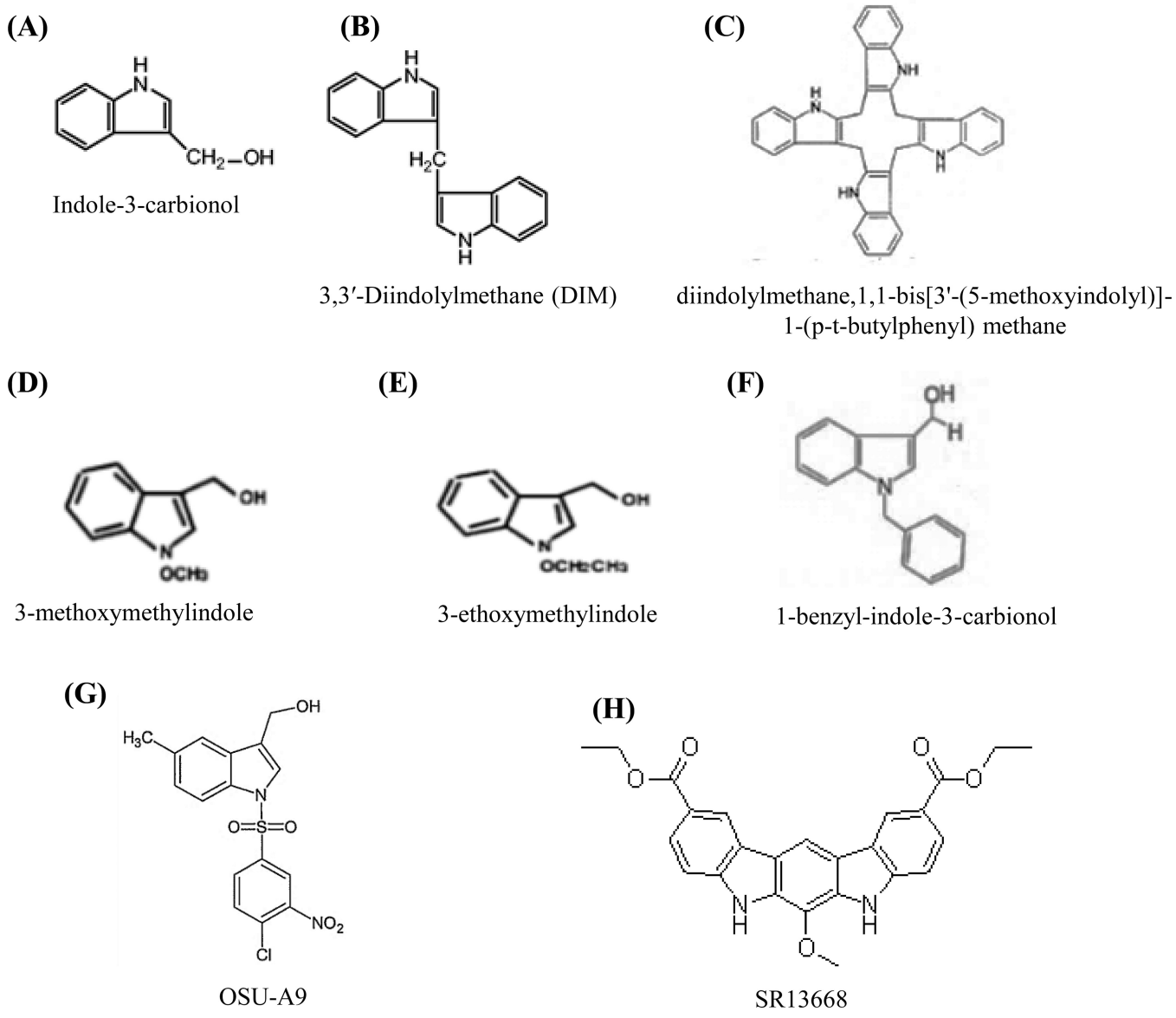


Fig. 11.
Indol-3-carbionol and its structural analogs.

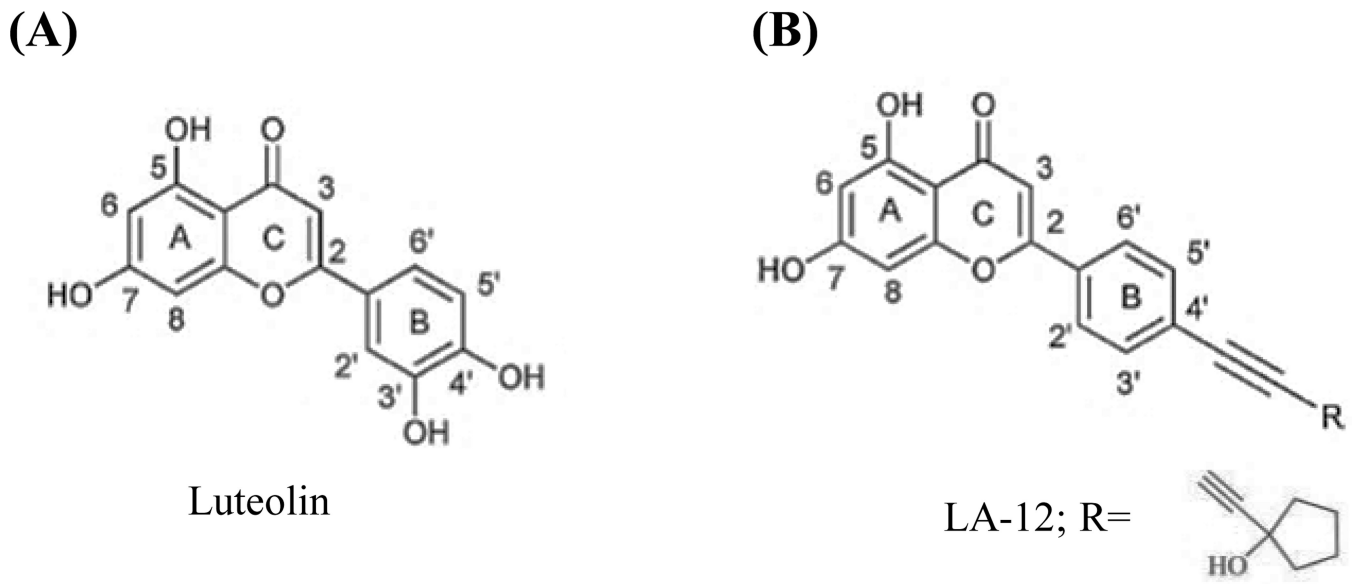


Fig. 12.
Luteolin and its structural analogs.

Table 1

Phytochemicals and their cellular targets

Name	Sources	Targets	References
Fisetin	Onion, cucumber, apple, persimmon, strawberry	• Inhibits cell growth, EMT and invasion • Induces cell cycle arrest and apoptosis • Inhibits PI3K, AKT, mTOR, NFκB, MEK1/2, ERK1/2, Wnt, β-catenin, and MITF	[106, 108, 110–112]
EGCG	Green tea	• Inhibits cell growth, EMT and invasion • Induces cell cycle arrest and apoptosis • Inhibits NFκB signaling pathway	[124–127, 129, 130]
Resveratrol	Peanut, grape skin, mulberry	• Inhibits cell growth, EMT and invasion • Induces cell cycle arrest and apoptosis • Inhibits AKT, mTOR, NFκB, MEK1/2, ERK1/2, β-catenin, MITF, STAT3, c-kit, AP-1/JunD, c-Jun and α-MSH	[152,153,155–163,171]
Curcumin	Turmeric	• Inhibits cell growth • Induces cell cycle arrest and apoptosis • Inhibits PI3K, AKT, NFκB, ERK1/2 and STAT3	[185–203]
Proanthocyanidins	Cocoa, grape, apple, tea, red wine	• Inhibits cell growth • Inhibits NFκB and ERK1/2	[220–222]
Silymarin	Milk thistle	• Inhibits cell growth • Induces cell cycle arrest and apoptosis • Inhibits NFκB, MEK1/2, ERK1/2, β-catenin, STAT3, AP-1/JunD and c-Jun	[102,243,244]
Apigenin	Chicory, clove, apple, cherry, grape, beans, broccoli, celery, leeks, onion, barley, parsley, tomato, tea	• Inhibits cell growth • Induces cell cycle arrest and apoptosis • Inhibits PI3K, AKT, ERK1/2, MITF, MAPK p38 and JNK	[154,252–256]
Capsaicin	Chili pepper	• Inhibits cell growth, invasion and angiogenesis • Induces cell cycle arrest and apoptosis • Inhibits PI3K, AKT, mTOR and NFκB	[268, 270–273]
Genistein	Soybean	• Inhibits cell growth and invasion • Induces cell cycle arrest and apoptosis • Inhibits signal transduction: AKT, MAPK p38 and JNK	[289–302]
Indole-3-carbinol	Broccoli, cauliflower, Brussels sprouts	• Inhibits cell growth • Induces cell cycle arrest and apoptosis • Inhibits AKT and MITF	[325–327]

Name	Sources	Targets		References
Luteolin	Carrot, pepper, celery, olive, peppermint, thyme, rosemary, oregano	•	Inhibits cell growth	[343–350]
		•	Induces cell cycle arrest and apoptosis	
		•	Inhibits α-MSH	