Chapter 8
Natural Compounds Are Smart Players in Context to Anticancer Potential of Receptor Tyrosine Kinases: An In Silico and In Vitro Advancement

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Abstract Cancer is the ruling cause of mortality worldwide. Chemotherapeutic toxicity and drug resistance have provided impulsion for the formulation of new anticancer agents. Receptor tyrosine kinases (RTKs) are the most activated cell surface receptors for copious polypeptide growth factors, cytokines, and hormones that play a considerable role in cancer initiation, promotion, and progression. Natural products are a prime source of new anticancer drugs and their leads. The objective of computer-aided drug design (CADD) is to enhance the set of compounds with prudent active drug-like properties and eliminate inactive, toxic, poor absorption, distribution, metabolism, and excretion toxicity (ADME/T) compounds. In the present chapter, in silico advancement of anticancer natural compounds and molecular mechanisms of action of flavonoids, viz., genistein, myricetin, quercetin, luteolin, morin, kaempferol, catechin, and epigallocatechin gallate (EGCG), on RTK and PI3K signaling pathway attributing to their potential anticancer activity have been discussed.

Keywords Receptor tyrosine kinases • Cancer • Natural compounds • Computer-aided drug design

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8.1 Natural Products: Promising Resource for Cancer Drug Discovery

Cancer is the ruling cause of mortality worldwide, especially breast and prostate cancer. They are regarded as the most frequent cancer in women and men, respectively, second to skin cancer (Jakowlew 2006). The toxicity associated with drug resistance and poor prognosis in the current chemotherapeutics has provided the much-needed impulsion for the formulation of new anticancer agents (Biswas et al. 2006; Martin et al. 2011). Natural products are a prime source of new anticancer drugs and their leads. Anticancer drug development of natural origin including plants (vincristine, vinblastine, etoposide, and paclitaxel), marine organisms (cytarabine and aplidine), and microorganisms (dactinomycin and doxorubicin) added a new concept for drug discovery. Furthermore, various compounds recognized from fruits and vegetables have been used as anticancer therapy. Moreover, curcumin, resveratrol, genistein, and diallyl sulfide had a most promising anticancer activity in the different model and entered into the clinical trial. Traditional medicines owe their capability to exhibit various biological activities including anticancer potential. Furthermore, synthetic analogs of natural compounds with improved potency and safety might be prepared, thus portraying them as the beacon for cancer drug discovery. In fact, natural products are an inspiration for the majority of US Food and Drug Administration (FDA)-approved drugs. Another remarkable character is that natural products can also be prepared by synthesis and have played a mid-role in the drug development by providing challenging synthetic targets. Plants have large reservoir of potent, novel, and highly varied structures that are dubious to be synthesized in laboratories. Over the past many years, plants have been known to be a cornucopia of biologically active compounds including cocaine, digitalis, quinine, and muscarine (Kumar et al. 2013). Many of these active compounds are useful drugs such as anticancer agent paclitaxel (Taxol) from the yew tree and antimalarial agent artemisinin from *Artemisia annua*. Flavonoids comprise a significant group of polyphenolic compounds, which are primarily benzo-α-pyrone (phenyl chromone) derivatives, structurally diverse low molecular mass molecules (Kumar and Pandey 2013). Bioactive flavonoids have been found to be indispensable for the growth and development of plants, additionally providing the physical environment that proves to be essential for plant survival under stress circumstances. Among the various natural products, flavonoids have attracted more attention owing to their remarkable spectrum of pharmacological activities such as antioxidant, antiangiogenic, anti-inflammatory, and anticancer activity (Mishra et al. 2013; Kumar et al. 2014).

Lim et al. (2008) reported seven *Aspidosperma* indole alkaloids (jerantinine A to G) that were extracted from the *Tabernaemontana corymbosa* leaf (Lim et al. 2008). Jerantinine A has been reported for its potent cytotoxic activity against vincristine-resistant nasopharyngeal carcinoma cells and has the capability to inhibit cell cycle at G2M stage and polymerization of tubulin (Raja 2015; Raja et al. 2014). Furthermore, jerantinine B and E are also reported for their potent

anticancer activity with a variety of mechanisms including disruption of microtubule organization and induction of apoptosis in different human cancer cell lines (Frei et al. 2013, Qazzaz et al. 2016). Jerantinine B, δ-tocotrienol, and combined low-dose treatments induced a dose-dependent growth inhibition against U87MG and HT-29 cells indubitably disrupted the microtubule networks (Abubakar et al. 2016).

Astragalus membranaceus is an adaptogenic herb that belongs to Leguminosae family originating in Northern China and has been used to treat a range of disorders including chronic illnesses, metabolic disorders, compromised immunity, inflammation, and cancer. Furthermore, treatment with *A. membranaceus* supplemented injection with current chemotherapy was found to hamper the tumor growth, decrease the unavoidable side effect of chemotherapy, restore the impaired T cell functions, and improve the drug sensitivity of tumor cells (Cho and Chen 2009; Zou and Liu 2003). Moreover, *A. membranaceus* injection might efficiently encourage the immune response of tumor-bearing host that led to improve the anti-metastasis activity of dendritic cells in vivo (Dong and Dong 2005). Further, it was also reported that *A. membranaceus*-based medicine might augment the usefulness of platinum-based chemotherapy for advanced non-small cell lung cancer (McCulloch et al. 2006). A polysaccharide isolated from the radix of *A. membranaceus* was reported to increase tumor sensitivity and reduce chemotherapeutic toxicity. Further, it was reported that treatment of *A.* polysaccharide integrated with vinorelbine and cisplatin had appreciably enhanced QOL in patients with advanced NSCLC compared with vinorelbine and cisplatin alone (Guo et al. 2012). Cho and Leung (2007a, b) reported that administration of *A. membranaceus* root fraction in tumor-bearing mice and cyclophosphamide-treated mice (in vivo) could reestablish the depressed immune functions. Thus, *A. membranaceus* could reveal immunomodulating and immune-restorative effects, both in vitro and in vivo (Cho and Leung 2007a, b, c). Furthermore, it was reported that the root of *A. membranaceus* was proficient to induce monocytic differentiation of both human and murine cells. Moreover, in vivo administration of *A. membranaceus* fraction could reestablish the depressed mitogenic response in tumor-bearing mice. Moreover, roots of this plant have polysaccharides (UV-absorbing compounds) which may have potential in protecting against solar-induced skin damage (Curnow and Owen 2016).

Identification and development of anticancer agents from the natural product by computer-aided high-throughput virtual screening (HTVS) and extra precision (XP) molecular docking has been well documented. In silico screening approach is the primary technique for identification of natural products as inhibitors of target protein and predicting their interactions. Examples of natural compounds that have been reported as anticancer properties identified by using HTVS and XP molecular docking are represented in Table 8.1.

Table 8.1 Anticancer natural compounds identified by HTVS and XP

Agents	Targets	References
Wortmannin	Wild-type and mutant PIK3CA	Kuete et al. (2015) and Dan et al. (2010)
Noscapine derivatives	Microtubule	Santoshi et al. (2014) and Naik et al. (2012)
Hinokiflavone	MMP-9	Kalva et al. (2014)
Combretastatin	Microtubule-destabilizing	Do et al. (2014) and Abolhasani et al. (2015)
Xanthone derivatives	DNA topoisomerase IIα	Alam and Khan (2014) and Verbanac et al. (2012)
Camptothecin	RAD9	(Prasad et al. (2013) and Yamazaki et al. (2004)
Linarin	CDK4	Meshram et al. (2012)
Violacein	Estrogen receptor	Meshram et al. (2012)
Hydroxycinnamic acid	MMP-2 and MMP-9	Wang et al. (2012a)
S-Adenosylmethionine	S-Adenosylmethionine	Taylor et al. (2009)
De novo drug design	c-Met tyrosine kinase	Chen (2008)
Sulfobenzoic acid	Transformylase	Xu et al. (2004)
Genistein	Acetylcholinesterase	Fang et al. (2014)
Quercetin	Inducible nitric oxide synthase	Singh and Konwar (2012)
Rutin and myricetin	α-Glucosidase	Hee and JuSung (2014)

8.2 RTK Signaling Inhibitors as Promising Anticancer Agent

RTKs play a prominent role in blood cancer and solid tumors as they are the most activated cell surface receptors for numerous growth factors, cytokines, and hormones (Robinson et al. 2000). They have been shown not just to be the key regulators of normal cellular processes but additionally to play a critical role in the growth and development of various cancers (Singh and Bast 2014a). There are two types of RTK family, first containing the transmembrane domain and second not possessing transmembrane domains (Hubbard and Till 2000). Overexpression of RTKs has been reported in numerous cancers, including non-small cell lung cancer and breast and prostate cancers. RTKs comprise of many protein molecules including EGFR, insulin receptor (IR) and insulin-like growth factor 1 (IGF1R), and vascular endothelial growth factor receptors (VEGFR). They have covalently bound heterotetramer protein consisting of two extracellular α-subunits and two transmembrane β-subunits.

Ligand-receptor interactions induce conformational changes that led to activate autophosphorylation of a cascade of tyrosine residues, ultimately resulting in activation of the PI3K pathway and rat sarcoma (RAS) pathway that is participated

Table 8.2 Examples of anticancer natural compounds as inhibitors of RTK signaling proteins

Natural compounds	Targets	References
Cyclopentyl-pyrimidine	IGF1R	Aware et al. (2015)
Oxindole-based inhibitors	FGFR1	
Platycodin D	VEGFR2	Luan et al. (2014)
ZINC natural database	VEGFR2	Li et al. (2014)
Genistein	EGFR	Yuan et al. (2008)
Quercetin	PDK1, PI3K, and mTOR	Singh and Bast (2014b)
Quercetin	EGFR and mutated EGFR	Singh and Bast (2014a)
Curcuminoid analogs	HER2	Yim-Im et al. (2014)
Alkaloids/flavonoids	PI3K	Jackson and Setzer (2013)
Curcumin derivatives	STAT3	Kumar and Bora (2012)
Natural compounds	STAT3	Liu et al. (2014)
Morin, myricetin, and EGCG	STAT3, IR, EGFR, and AR/ER	Singh and Bast (2014a, b and 2015a, b, c)

in cellular growth and metabolism. PI3K, Akt, PDK1, and mTOR are activated by a number of cellular processes including expression of oncogenes and inactivation of tumor suppressor genes, tyrosine kinase receptors, and G-protein coupled receptors (Frasca et al. 2008). Numerous anticancer natural compounds that have been reported as inhibitors of RTK signaling proteins demonstrated by using CADD are given in Table 8.2.

Flavonoids exhibit anticancer activity by synchronizing the expression of EGFR, VEGF, and matrix metalloproteinases (MMPs) in addition to inhibiting NF-κβ and PI3K signaling pathways (Gu et al. 2013). VEGFR activation led to angiogenesis which is closely linked to the development of cancer including prostate, breast, lung, and hepatocellular carcinoma (Chu et al. 2013; Folkman 2002; Hicklin and Ellis 2005; Huang et al. 2011; Tanno et al. 2004). Encouraging strategy for combating cancer by inhibiting abnormal angiogenesis and employing monoclonal antibodies, ribozymes, and TRK inhibitors are currently in clinical trials (Arora and Scholar 2005; Ferrara et al. 2004; Saini and Hurwitz 2008). Oral tyrosine kinase inhibitors, namely, sorafenib, sunitinib, and pazopanib, have been endorsed by the USFDA for the treatment of diverse cancer (Wang et al. 2012b). Various in vitro, in vivo, and preclinical findings convincingly proclaim the use of dietary products in the prevention and treatment of cancer also (Amin et al. 2009).

Cancer is an extremely heterogeneous malignancy, with its signal pathways evince a complex array of cross signaling pathways. Appropriately, when blocking the key signal transduction pathways, the single-targeted drugs can also activate the other pathways that led to increasing cell proliferation. Therefore, multitargeted drugs have the better option for future drug discovery. RTK inhibitors have played an increasingly significant role in the treatment of various cancers. Recently, published phase clinical III trials have exposed potential efficacies of these drugs. Multitargeted TKIs have been regarded as promising agents for various cancers due to their potential antitumor mechanisms. Single-targeted drugs have poor efficiencies for most cancer patients, while they may be highly productive in certain cancer

patients. Thus, it is imperative to identify populations that are suitable for TKIs (Zhou 2012). Moreover, synergistic action by multi-targeting compounds produces a new strategy for discovering anticancer drugs for cancer drug resistance (Zhang et al. 2014a). In this context, obstruction of many essential kinases at the level of receptors or downstream serine/threonine kinases may assist to optimize the most anticancer therapeutic sake.

8.3 Multidrug Resistance Development in Cancer

Different critical factors are responsible for the development of cancer multidrug resistance such as (1) mutations in target proteins, (2) augmented action of drug efflux pumps (ATP-binding cassette superfamily), (3) decreased drug influx, and (4) distorted expression of apoptosis and (5) anti-apoptotic proteins (Costantino and Barlocco 2013). ABC transport molecules are expressed on the membranes of cellular vesicles and affect the biochemical and biophysical properties, i.e., ADME/T of chemotherapeutics. Mechanism such as insensitivity to drug-induced apoptosis and induction of drug detoxification perhaps play a vital role in earning of anticancer drug resistance. Overactivity of ABC transporters in cancer cells modulates anticancer drug resistance. In this context, an ongoing effort to succeed therapies could either block or inactivate these transporters. This may lead to increase the anticancer drug concentration within the cells. Bioactive flavonoids have been found to be indispensable for the growth and development of plants, additionally providing the natural environment that proves to be essential for plant survival under stress condition. Among the various natural products, flavonoids have attracted more attention owing to their remarkable spectrum of pharmacological activities such as antioxidant, antiangiogenic, anti-inflammatory, and anticancer activity.

8.4 CADD

It is broadly accepted that drug discovery and development are risky, costly, and time- and resource-consuming processes. A variety of cancer drugs are small compounds designed to bind and modulate the biological action of the receptors. Molecular docking inheres in three key consecutive goals: pose prediction, virtual screening, and binding affinity evaluation. There is an ever improved endeavor to apply the computational method for drug design, development, and optimization in the field of chemical and biological sciences. In the modern arena, computer-aided or in silico molecular drug development is being utilized to accelerate and facilitate hit identification and optimization of the absorption, distribution, metabolism, excretion, and toxicity profile. Recently, researchers are dynamically involved in the development of more sophisticated computational tools that will ameliorate

potency and efficiency of the drug development process, decrease the use of animals, and increase accuracy of pose predictability. The rapid expansion of CADD by the advancement of computational software (AutoDock, DOCK, GOLD, and Maestro), identification of molecular targets, and an expanded database of the publicly accessible target crystal structure of the protein provided the preeminent environment for drug discovery. CADD is being exploited to identify hits, pick leads, and optimize leads, i.e., transform biologically active compounds into good drugs by enhancing their physicochemical, pharmaceutical, and ADME/T properties. HTVS is used to discover novel agents from different chemical scaffolds by searching commercial, public, and private databases. It is deliberated to reduce the size of chemical space and thereby allow cornerstone on more promising candidates for lead discovery and optimization. The aim of CADD is to enhance the set of compounds with drug-like properties and eliminate compounds with inactive, toxic, poor ADME/T. In other words, in silico modeling is used noticeably to minimize time and resource necessities of chemical synthesis and biological in vitro and in vivo testing (Guedes et al. 2014; Kapetanovic 2008).

Natural products are a significant source of bioactive compounds for drug breakthrough. However, their utilization in drug discovery has somehow diminished because of barriers to the screening of natural products against anticancer targets. In another study, Kapetanovic (2008) reported that the estimated time and cost of new drug bringing to market differ, by 7–12 years and $ 1.2 billion. Also, 5 out of 40,000 compounds experimentally validated in animals reach primary human testing. Furthermore, only one of five compounds achieves approval for clinical studies (expected). Taking in these barriers for drug development, here we discuss the strategies for in silico screening of natural compounds that strap up the current technology that may help to abridge these barriers (Harvey et al. 2015). Commonly used computational approaches for screening of natural products against anticancer targets include (1) target identification and validation (reverse docking, protein structure prediction, target druggability, probe design, and chemical sensing) and (2) lead discovery and optimization (molecular docking, de novo design, designs virtual library based on pharmacophore, quantitative structure-activity relationship models, and sequence-based method for phosphorylation site prediction). Approaches used for target identification, validation, lead discovery, and optimization are depicted in Fig. 8.1.

1. *Target identification and validation*

- Reverse docking

Due to increased number of well-known protein structures (NMR and 3D crystallographic), a new molecular docking method called reverse docking comes in a picture, in which docking is carried out by probing a protein database instead of a compound database. Reverse docking is proving to be an influential tool for identification and validation of small molecules into a set of target proteins, in addition to the lead discovery and optimization stages of the drug development cycle (Chen and Ung 2001), for example, Indock, a reverse docking platform to study drug toxicity, and TarFisDock, used to identify drug targets (Li et al. 2006).

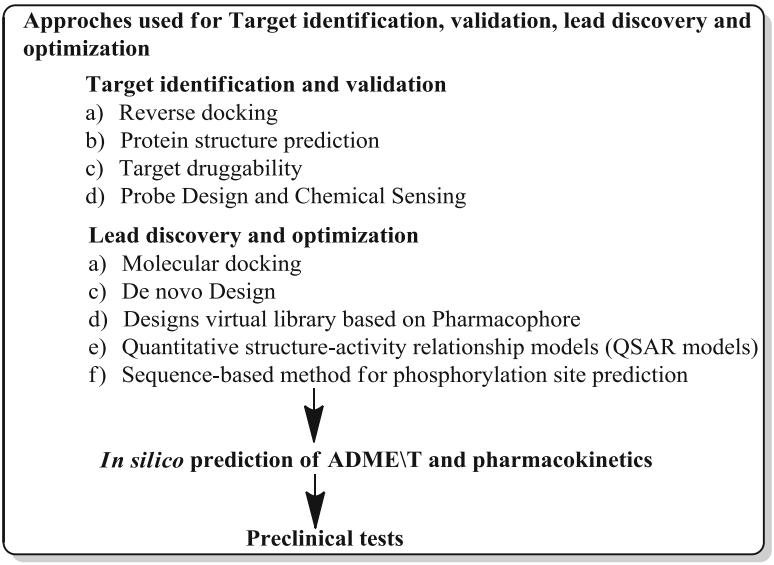

Fig. 8.1 Outline of CADD-based drug designing and development

- Protein structure prediction

Over the past genomic decade, the whole genome sequencing projects have produced a huge quantity of protein sequence data, which led to fill the gap between protein sequence and structure. Furthermore, in vitro experimental determination of a protein structure and function is rigorous, time-consuming, and expensive. Therefore, the use of computational tools for conveying structure to a protein represents the most proficient option for experimental methods (Neerincx and Leunissen 2005). To overcome this problem, a plethora of computerized methods are accessible (online servers and software) to predict protein primary, secondary, and tertiary structure from the amino acid sequence (Fischer 2006; Pavlopoulou and Michalopoulos 2011). A variety of protein databases provided information regarding amino acid sequences derived from nucleotide databases such as GenPept, RefSeq, the protein information resource, and the UniProt knowledgebase (Bairoch et al. 2005; Pruitt et al. 2007; Wu et al. 2002).

- Druggability

Druggability is the property of target molecules (proteins and nucleic acids) that elicits a positive clinical response when bind with a compound. It is known that best drug target should have the following properties: approving capability for high-throughput screening and capability to change a disease physiology and differential expression of target molecules (Bakheet and Doig 2009). Due to the lack of knowledge about the molecular mechanism of disease and target identification, experimentally an assessment of proteins for their druggability is a discouraging job and makes the convoluted situation. In

this context, with the aid of progress information such as protein-protein interaction and metabolic and gene regulatory networks, computational models can predict drug targets with high sensitivity and in lesser time (Costa et al. 2010; Kandoi et al. 2015).

- Chemical probes

Chemical probes (fluorescence resonance energy transfer-based probes and MRI probes) are crucial tools for evaluation of biochemical processes and detection of hazardous compounds in cells. Therefore, the development of chemical probes provided a lot of information regarding appreciation of disease marker. Recently, fluorescent-based probes have the best consideration because they are easy and more sensitive to predict protein targets (Jun et al. 2011; Kikuchi 2010).

2. *Lead discovery and optimization*

- Molecular docking

The discovery of potent drug targets has regular increases in the last few decades due to the expansion of genomic and proteomics techniques. Experimental and computational tools are dynamically applied to lead identification and optimization. The lead molecules are capable of modulating the biological function of the target proteins. Various molecular docking techniques such as HTVS, XP, and induced molecular docking technology prompt identification of drug-like leads.

- Designs virtual library based on pharmacophore

Pharmacophore models are a geometrical description of the chemical functionalities and can be generated using two different approaches depending on the input data employed for model construction (Güner and Bowen 2014). (1) Structure-based modeling and the interaction pattern of a molecule and its targets are extracted from experimentally determined ligand-protein interactions (Kaserer et al. 2015). (2) In the case of ligand-based modeling, 3D structures of two or more known compounds are aligned, and pharmacophore character is shared among these training set molecules.

- De novo design

Biochemical and organic model builder is used to develop molecules by adding layers of substituents to a core molecule that has been positioned in a binding site.

- Quantitative structure-activity relationship (QSAR)

The aims of quantitative structure-activity relationship (QSAR) analysis are (1) to predict biological activity (biological/toxicological) and physicochemical properties of compounds (2) and to rationalize the mechanisms of action within a series of chemicals employing the interdisciplinary information of chemistry, mathematics, and biology. Numerous studies have attempted to correlate mathematically the property of molecules using different computationally derived

quantitative parameters termed as descriptors. There are two types of QSAR used in drug discovery: (1) 2D-QSAR and (2) 3D-QSAR (Divakar and Hariharan 2015).

- Sequence-based method for phosphorylation site prediction

Kinase-mediated phosphorylation is one of the imperative posttranslational modifications. Cell signaling defects linked with protein phosphorylation are associated with cancer initiation and progression. Therefore, identification of protein phosphorylation sites is essential for studying disease finding. However, experimental recognition of phosphorylation sites is costly and labor intensive. Computational methods are helpful tools for phosphorylation site identification (sequence-based method for serine, threonine, and tyrosine phosphorylation site) and afford information regarding cell signaling (He et al. 2012; Trost and Kusalik 2011).

- ADME/T modeling for drug design

In recent decades, in silico absorption, distribution, metabolism, excretion (ADME), and toxicity modeling are used as a tool for computer-aided drug design in pharmaceutical research. Recently, various ADME/T-related prediction models have been reported by many software and online predictors. Due to easy compound screening, low-cost nature of these models permits more rationalized drug identification and their structural optimization in addition to the parallel investigation of bioavailability and activity. However, the modern in silico approaches still need additional progress (Wang et al. 2015).

8.5 Flavonoids: Molecular Mode of Action

8.5.1 Genistein

Genistein is a phytoestrogen soy product belonging to the class of isoflavones predominantly found as glycosylated form in plants. Its effect has been reported for copious biological processes such as growth and development that were found to result in metabolic alterations at the cellular level. Furthermore, it was established that ingestion of dietary genistein also led to changes in metabolic hormones including insulin, leptin, thyroid, adrenocorticotropic, cortisol, and corticosterone (Takeda et al. 1997; Zhou et al. 2014). Experimental evidences collected over the past few decades have upheld the information that inhibition of cancer cell growth by genistein is conciliated via the inflection of RTK signaling pathways that result in control of cell cycle and apoptosis (Chen et al. 2013; Chung et al. 1997; Niu et al. 1999; Shim et al. 2010; Siddiqui et al. 2004; Walker et al. 2000). Consequently, it has been observed that antiproliferative activity of daidzein and genistein may be linked with the oncogene products such as estrogen receptor α and TK c-erbB-2 expression in breast cancer cells. As evident in several reports,

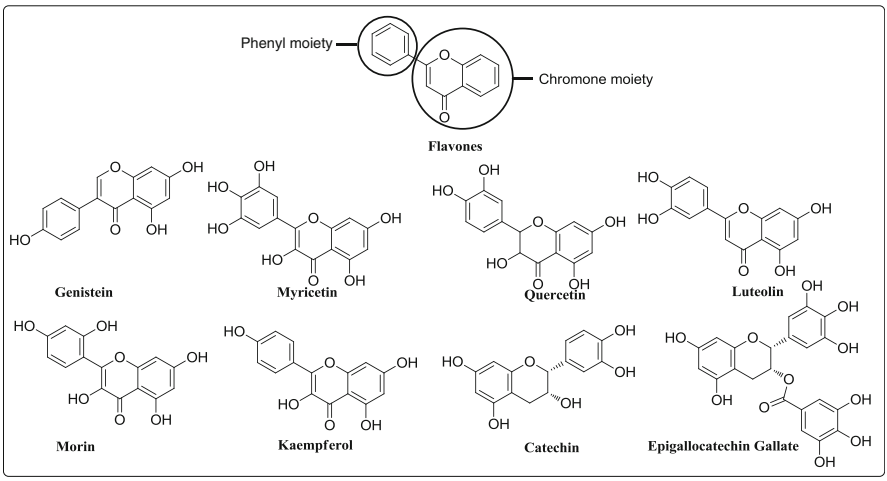

Fig. 8.2 Molecular structure of flavonoids

genistein impedes the activation of PI3K and MAPK signaling molecules which are known to perpetuate a homeostatic equilibrium between cell growth and apoptosis in nasopharyngeal carcinoma cells (Ding et al. 2003; Kerns and Di 2010; Mechoulam and Pierce 2005). It is reported that genistein effectively inhibits the activity of downstream targets such as Src, Akt, and glycogen synthase kinase-3β (Müller et al. 2001). Molecular structures of active multitargeted RTK signaling inhibitor flavonoid are represented in Fig. 8.2.

8.5.2 Quercetin

Quercetin belongs to flavonoids that play an important role in cancer prevention. Quercetin inhibited EGFR cell signaling with an activation of a forkhead family of transcription factor FOXO1 activation. Many reports confirm that quercetin is an efficient anticancer agent that induces apoptosis and decreases cell proliferation in oral cancer cells overexpressing EGFR (Huang et al. 2013). Furthermore, it was also observed that quercetin may induce apoptosis and reduce cell proliferation in HeLa cells via the AMPK-induced HSP70 and downregulation of EGFR (Jung et al. 2010). In vitro and in vivo experiments revealed that quercetin could inhibit the proliferation and induce apoptosis in cancer cells (Huang et al. 2013; Lyne 2002). Moreover, quercetin is observed to arrest the cell cycle at the G0/G1 phase and induce apoptosis in PC3 cells via intrinsic apoptotic stimuli that led to DNA damage (Liu et al. 2012a, b).

Genistein, quercetin, luteolin, morin, and kaempferol anticancer properties in different cancer cells are represented in Table 8.3.

Table 8.3 Genistein, quercetin, luteolin, morin, and kaempferol anticancer properties in different cancer cells

Agents	Tumors	References
Genistein	Breast cancer	Parra et al. (2016)
	Breast cancer	Fang et al. (2016)
	Colorectal cancer	Qin et al. (2015)
	Pancreatic cancer	Suzuki et al. (2014)
	Breast cancer	Xie et al. (2014)
Quercetin	Liver cancer cells	Wu et al. (2014)
	Liver cancer cells	Olayinka et al. (2014)
	Anticancer	Pandey et al. (2015)
	Anticancer	Brito et al. (2015)
	Colon cancer	Refolo et al. (2015)
Morin	Colon cancer	Hyun et al. (2015)
	Leukemia cell	Karimi et al. (2013)
	Anticancer	Neves and Kwok (2015)
	Leukemia cell	Park et al. (2014a)
	Osteoblast and breast tumor	Naso et al. (2013)
Luteolin	Head and neck cancer	Majumdar et al. (2014)
	Anticancer	Lin et al. (2008)
	Lung cancer cells	Ma et al. (2015)
	Gastric cancer	Lu et al. (2015)
	Anticancer	Sak (2014)
Kaempferol	Cervical cancer	Tu et al. (2016a, b)
	Esophageal cancer	Tu et al. (2016a, b)
	Anticancer	Kadioglu et al. (2015)
	Lung cancer	Park et al. (2014b)
	Anticancer	Batra and Sharma (2013)

8.5.3 Morin

Morin is a flavone that exhibits antiproliferative, antioxidant, and anti-inflammatory activity by modulating NF-κβ signaling pathway. It has been observed to inhibit the NF-κβ-dependent gene expression activated by tumor necrosis factor (TNF) and the p65 subunit of NF-κβ. It enhances apoptosis and reduced invasion via downregulation of MMP2 and MMP9. These effects were correlated with enhancement of apoptosis induced by TNF and chemotherapeutic agents (Wang et al. 2009). Furthermore, in vitro and in vivo findings indicate that morin possesses anti-inflammatory, anti-angiogenesis, and antiproliferative activity by supporting suppression of diethylnitrosamine-induced hepatocellular carcinoma cells via downregulation of MMP2 and MMP9 (Masuda et al. 2003). It was also observed that morin induces apoptosis in HL-60 and hepatocellular cells by activation of the cysteine-aspartic acid protease-3 (caspase-3) (Kuo et al. 2007; Luo et al. 2001; Sivaramakrishnan and Devaraj 2010).

It has been suggested that morin prevents acute liver damage by inhibiting the production of the pro-inflammatory cytokine (Park et al. 2010).

8.5.4 *Luteolin*

Luteolin is one of the most widespread naturally occurring flavonoids present in edible plants. It has been reported that luteolin suppresses VEGF-induced phosphorylation of VEGF2R in prostate cancer cells (Liu et al. 2012a, b). Luteolin exhibited cyclin-dependent kinase cell cycle arrest in breast cancer cells. Further, it has been reported that luteolin down-regulate the EGFR mRNA expression followed by the inhibiting MAPK activation (Morales and Haza 2012). Luteolin exhibited cyclin-dependent kinase cell cycle arrest in breast cancer cells. Further, it has been reported that luteolin down-regulate the EGFR mRNA expression followed by the inhibition of MAPK activation (Azevedo et al. 2015; Kim et al. 2012; Lin et al. 2008; Lopez-Lazaro 2009; Maggioni et al. 2014; Phillips et al. 2011; Sak 2014; F. Sun et al. 2012; Xu et al. 2013; Zhang et al. 2010, 2014a, b, 2015). Luteolin could sensitize cancer cells to inhibit cell proliferation and induce apoptosis and cell cycle arrest through suppressing cell survival pathways such as PI3K and MAPK in colon cancer cell, epithelioid cancer, pancreatic cancer cells, hepatoma cells, breast cancer cells, lung cancer xenograft models, and gastric carcinoma xenografts in nude mice (Azevedo et al. 2015). Luteolin also inhibited hypoxia-induced cell proliferation, motility, and adhesion via inhibiting the expression of integrin β1 and focal adhesion kinase (Wang et al. 2014).

8.5.5 *Kaempferol*

Kaempferol is a yellow crystalline solid, slightly water-soluble natural polyphenol belonging to the group of antioxidant flavonoids. Moreover, numerous studies showed that consumption of kaempferol containing foods led to reduced risk of cancer and cardiovascular diseases. Furthermore, numerous preclinical studies have demonstrated that kaempferol and some glycosides of kaempferol have extensive pharmacological activities including antioxidant, anti-inflammatory, anticancer, neuroprotective, antidiabetic, analgesic, and antiallergic (Prasad et al. 2013). Moreover, the cytotoxicity and resistance of anticancer drugs that conjugate with glutathione may be influenced by long-term intake of kaempferol (Sivashanmugam et al. 2013). It is reported that oxidative stress induced by kaempferol in chronic myelogenous leukemia cells (K562) and promyelocytic leukemia cells (U937, K562, and U937) affects the inactivation of PI3K signaling pathways which may lead to cell death. Kaempferol has been reported to induce apoptosis via endoplasmic reticulum stress and mitochondria-dependent pathway in osteosarcoma U2OS cells. In vivo efficacy of kaempferol was assessed in BALB/nu/nu mice inoculated

with U2OS cells and indicated inhibition of tumor growth by reducing cell proliferation and inducing apoptosis. Furthermore, it inhibits the growth of human osteosarcoma cells both in vivo and in vitro (Meshram et al. 2012; Prasad et al. 2013). Kaempferol and quercetin were known to induce apoptosis and cell cycle arrest in various oral cancer cell lines including SCC1483, SCC-25, and SCC-QLL1 via caspase-3-dependent activity. Kaempferol induces apoptosis through oxidative stress and induces G2/M cell cycle arrest in glioblastoma, HeLa, and leukemic cell lines (Taylor et al. 2009; Xu et al. 2004). Kaempferol is known to reduce cell proliferation through downregulation of oncoprotein c-Myc and promoting apoptosis and cell cycle arrest in ovarian cancer cells (Luo et al. 2010).

8.5.6 Green Tea

Green tea is a wonderful beverage with potential health benefits made from the leaves of *Camellia sinensis* via minimum oxidation processing with abundant polyphenols, including epigallocatechin gallate (EGCG), epicatechin gallate (ECG), epigallate catechin (EGC), and epicatechin (EC) targeting multiple signaling pathways that lead to anti-oxidative and anticarcinogenic potential (Kadioglu et al. 2014; Khan et al. 2006). Multitargeted anticancer activities of EGCG have been demonstrated by using in silico, in vitro, and in vivo study represented in Table 8.4.

EGCG affect numerous molecular targets involved in cancer cell proliferation and survival; however, polyphenolic catechins such as EGCG exhibit poor oral bioavailability. The consumption of green tea has been recommended for chemoprotective activity. Previous studies have established that active anticancer constituent in green tea is EGCG with the anticancer activity highlighted in various in vitro and in vivo studies. The anticancer activity of EGCG may be accredited to the combinatory effects on multiple targets that are determinant for cell proliferation and apoptosis (Alam and Khan 2014; Dennler et al. 2002; Kalva et al. 2014; Kuete et al. 2015; Santoshi et al. 2014; Xu et al. 2004). A number of reports confirm that green tea reduces cell proliferation and sensitizes the cell to apoptosis, ultimately leading to cancer cell growth inhibition in diverse cancer cells including colorectal and hepatocellular carcinoma, SW480 colon cancer, SV40 virally transformed WI38 human fibroblasts (WI38VA), prostate cancer, and Ishikawa cells (Li et al. 2014; Liu et al. 2014; Mayer and Gustafson 2004, 2008; Sun et al. 2014; Yim-Im et al. 2014). Interestingly, green tea showed anticancer property in colorectal and hepatocellular carcinoma cells via regulating the activation of tyrosine kinase EGFR (Khan et al. 2006; Shimizu et al. 2011; Shimizu et al. 2008). Furthermore, it was reported that EGCG has potential inhibitory effects on tumor angiogenesis, induced by IGF1 in non-small cell lung cancer cells via downregulation of HIF-1α and VEGF expression. EGCG inhibiting tumor invasion and angiogenesis underlines the role of green tea as a cancer chemopreventive agent (Jackson and Setzer 2013). EGCG treatment was found to inhibit UV-induced

Table 8.4 EGCG anticancer properties in different cancer cells

Agent	Tumors and tumor cells	References
(−)-EGCG	Nasopharyngeal carcinoma cells	Fang et al. (2015)
(−)-EGCG	Lung cancer	Zhang et al. (2015)
(−)-EGCG	Squamous cell carcinoma	Irimie et al. (2015)
(−)-EGCG	HL-60 promyelocytic leukemia cells	Saiko et al. (2015)
(−)-EGCG	Head and neck tumor	Masuda et al. (2003)
(−)-EGCG	Mouse embryonic fibroblast cells	Yagiz et al. (2007)
(−)-EGCG	Human osteogenic sarcoma (HOS) cells	Ji et al. (2006)
(−)-EGCG	Laryngeal squamous carcinoma cells	X. Wang et al. (2009)
(−)-EGCG	Nasopharyngeal carcinoma cells	Luo et al. (2001)
(−)-EGCG	Renal cell carcinoma	Gu et al. (2009)
(−)-EGCG	Hypopharyngeal carcinoma cells	Park et al. (2010)
(−)-EGCG	Pancreatic cancer cells	Z. Wang et al. (2008)

epidermal lipid peroxidation, decrease antioxidant enzyme glutathione peroxidase activity, and increase catalase activity against exposures to UV light in the human skin (Kumar and Bora 2012). Catechin induces apoptosis and cell cycle arrest and reduces cell proliferation via deviated antioxidant parameters including superoxide dismutase, catalase, and lipid peroxidation in HepG2 cells (Amaral et al. 2014).

8.5.7 Myricetin

Myricetin is a naturally occurring phenolic flavonol found in red wine, fruits, vegetables, and herbs possessing antioxidant and anti-inflammatory activity. In vitro investigations demonstrate that in high concentrations, it can improve lipoproteins such as low-density lipoprotein cholesterol. Myricetin was observed to ameliorate inoperative insulin signaling via β-endorphin signaling in the skeletal muscles of fructose-fed rats. It enhances the secretion β-endorphin, followed by peripheral μ-opioid receptor activation which leads to amelioration of impaired insulin receptor signaling (Lee et al. 2004; Yamaguchi et al. 1995). JAK1/STAT3 pathway activated by cytokine and growth factor including insulin, IGF1, and EGF has been recommended to play a significant role in cell proliferation, differentiation, and cell migration (Simon et al. 1998; Vela et al. 2015). It was reported that myricetin directly binds to JAK1/STAT3 molecules to inhibit cell transformation in EGF-activated mouse $JB6P^{+}$ cells (Kumamoto et al. 2009). The multitargeted anticancer activity of myricetin has been demonstrated by using in silico, in vitro, and in vivo study represented in Table 8.5.

Table 8.5 Myricetin anticancer potential in different cancer cells

Agent	Tumors and tumor cells	References
Myricetin	Esophageal carcinoma	Wang et al. (2014)
Myricetin	breast cancer	Zhang et al. (2014a, b)
Myricetin	Lung cancer	Zhang et al. (2014a, b)
Myricetin	Colon cancer cells	Kim et al. (2014)
Myricetin	Squamous cell carcinoma	Maggioni et al. (2014)
Myricetin	Prostate cancer cells	Xu et al. (2013)
Myricetin	Pancreatic cancer cells	Phillips et al. (2011)
Myricetin	Hepatocellular carcinoma	Zhang et al. (2010)
Myricetin	Gastric and ovarian cancers	Sak (2014)
Myricetin	Leukemia	Morales and Haza (2012)
Myricetin	Bladder cancer	Sun et al. (2012)
Myricetin	Glioblastoma cells	Siegelin et al. (2009)

8.6 Conclusions and Outlook

Insulin, IGF, EGF, and VEGF growth factors are crucial to the growth and regulation of cancer cells. Receptors for these growth factors are a striking target to combat cancer. Moreover, binding of ligands to receptor molecules induces conformational changes and activates autophosphorylation of a cascade of tyrosine residues of small protein molecules such as STAT3. PI3K pathway is one of the most habitually activated signal transduction pathways distant from RAS that plays a significant role in cellular growth and metabolism. PI3K, Akt, PDK1, and mTOR are activated by a number of biological processes including expression of oncogenes and inactivation of tumor suppressor genes.

A vast scientific data has accumulated, elucidating the molecular mechanisms of cancer development and the action of anticancer agents in cancer prevention. These research findings have provided the basis for the identification of molecular mechanisms for cancer prevention and treatment. Notably, these discoveries have identified key molecular targets for screening and testing novel natural anticancer drugs that have fewer adverse side effects. However, despite increasing advances in drug discovery and preclinical testing, anticancer drug development remains a laborious, time-consuming process with limited success. This suggests a critical need to differentiate at an earlier stage of development between promising candidates and those less likely to be effective. Even though progress has been made in identifying important molecular targets and potential nontoxic anticancer agents, transitioning preclinical results into the clinic has been extremely challenging. Unfortunately very few compounds have shown real promise in clinical trials. The combination of two or more compounds that target multiple pathways simultaneously is a strategy that is rapidly gaining widespread acceptance. Researchers suggested that combinations of drugs that could block heterogeneous cancers by inhibiting multiple signaling pathways have also been revealed beneficial in clinical trials.

Furthermore, combinations of agents with natural compounds will probably require a lower dose of each compound which led to less toxicity and fewer side effects. In silico screening uses molecular docking programs that target molecules into the active site and then ranks molecules by their aptitude to interact with the target protein. Such computer-identified drug targets can be validated in vitro and in vivo using cell-based biochemical assays and animal studies as well.

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