Chapter 5
Plant-Derived Compounds in Cancer Therapy: Traditions of Past and Drugs of Future

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5.1 Introduction

Cancer has become a leading cause of morbidity and mortality worldwide, and contributed to approximately 8.8 million deaths in 2015 (WHO 2017), and it is projected that without any prompt action, the number of new cases will be increased by approximately 70% in the next two upcoming decades mostly in low- and middle-income countries. In this regard, inflammation is associated with numerous diseases and severe disorders, including rheumatoid arthritis, asthma, chronic inflammatory bowel diseases, type 2 diabetes, neurodegenerative diseases, and cancer (Scrivo et al. 2011). Furst and Zundorf (2014) reported that anti-inflammatory agents primarily contain glucocorticoids, nonsteroidal anti-inflammatory, and immune-suppressant drugs. While tremendous efforts have been made over the past decades to enhance the available therapeutic options, conventional therapy seems to be not effective due to undesirable side effects. For instance, chemotherapy using synthetic drugs causes unwanted side effects, such as bleeding, hair loss, myelotoxicity, and diarrhea (Breidenbach et al. 2003). Most of the anticancer agents exhibit a narrow therapeutic effect and lack selectivity towards cancer cells. Therefore, the

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discovery of new anticancer agent from natural products has drawn a great attention among scientists in both academia and industry.

Natural products play a vital role in anticancer therapy. There are over 500 bioactive constituents from microorganisms, marine plants, and terrestrial plants which have been identified to have antioxidant, antiproliferative, or anti-angiogenic properties to suppress the tumor proliferation (Orlikova et al. 2014). Collectively, 78.6% of all approved anticancer agents are derived from natural products, with only 21.4% being synthetic ones that are not related with nature. Many evidences suggest that nature plays a crucial role in modern therapy especially in the development of drugs from natural origins (Folmer et al. 2012; Orlikova et al. 2014).

Plants exert numerous bioactive metabolites and have received great demands in the field of pharmacology due to there curative properties (Moghadamtousi et al. 2013). They act as a central player in the development of sophisticated traditional medicine particularly against cancer diseases. Prominent plant-derived compounds, such as morphine, colchicine, quinine, pilocarpine, atropine, and/or theophylline, are vitally important in the current pharmacotherapy. Due to the development of organic synthesis, many plant-derived compounds have become the first leading structures in the history of drug development (Furst and Zundorf 2014). Several examples reported by Furst and Zundorf (2014) showed that vinblastine is originally from the Madagascar periwinkle (*Catharanthus roseus*), served as a valuable anticancer drug. Paclitaxel isolated from the Pacific yew (*Taxus brevifolia*), galantamine derived from Caucasian snowdrop (*Galanthus caucasicus*), and capsaicin from chili peppers (*Capsicum* species) are promising secondary plant metabolites. Plant-derived compounds are highly used as leading structures with chemical modifications. Some of them include salicylic acid (acetylsalicylic acid), morphine (scores of derivatives), artemisinin (artemether), dicoumarol (warfarin), and camptothecin (topotecan and irinotecan). Of particular interest in this chapter, we will highlight on the emerging role of plant-derived compounds and their anticancer activities. We also provide a cohesive representation of the literature on the underlying mechanisms of action involved in the pharmacological effects of these phytochemicals.

5.2 Inflammation: A Hallmark of Cancer

Based on the hallmarks of cancer and its characteristics, inflammation and the associated cell signaling pathways have drawn an interest recently. Inflammatory environment is a cause for cancer progression and development (Balkwill and Mantovani 2001). Abnormal cell proliferation was due to deoxyribonucleic acid (DNA) damage, where their growth rates are influenced by secretion of chemokines and cytokines and the growth factors produced by modification of inflammatory cells (Balkwill and Mantovani 2001; Prasad et al. 2010). This is supported by previous findings, which indicates that natural compounds can suppress this hallmark efficiently (Folmer et al. 2012).

5.3 Currently Used Anticancer Agents

5.3.1 Anti-angiogenesis Agents

Vascular endothelial growth factor (VEGF) is one of the crucial factors responsible for inducing angiogenesis, and most of the activities are primarily modulated by vascular endothelial growth factor receptor 2 (VEGFR-2). Therefore, most of the anti-angiogenic agents target either VEGFR-2 or VEGF (Weis and Cheresh 2011). Anti-VEGF agents, including pegaptanib, ranibizumab, and bevacizumab, are usually used in the treatment of multiple solid and hematological malignancies, choroidal neovascularization (CNV), and age-related macular degeneration (AMD) (Hefner and Gerding 2014; Marinaccio et al. 2014; Solomon et al. 2014). Tyrosine kinase inhibitors, including sorafenib, regorafenib, axitinib, and sunitinib, are targeting for VEGFR-2 receptors. Interestingly, anti-VEGF agents were shown not only as anti-angiogenic agent but also as potential therapeutic for asthma, chronic obstructive pulmonary disease (COPD), and diabetic macular edema (DME), as reported by Arevalo (2014), Bandello et al. (2014), and Olivieri and Chetta (2014), suggesting a wide ranging functional potentials of anti-VEGF agents. In addition, some of the fusion proteins suppress the angiogenic molecule activities by trapping molecules effectively and inhibit the synthesis of these factors via suppression of mammalian target of rapamycin (mTOR), heat-shock protein 90 (HSP90), and cyclooxygenase (COX) pathways (Lockhart et al. 2010).

Although these anti-angiogenic agents showed a positive effect in inhibition of pathological angiogenesis, severe side effects arising from cancer patients are debilitating and result in depriving these patients in optimum and positive effects of anti-angiogenic therapy (Al-Husein et al. 2012; Elice and Rodeghiero 2012; Faruque et al. 2014). Anti-VEGF agents injected in AMD patients via intravitreal were associated with an increased risk of bleeding and cardiovascular toxicity (Elice and Rodeghiero 2012; Thulliez et al. 2014). Other undesirable adverse effects, including hepatic, cutaneous, hematological, and renal toxicities and malignant hypertension, have also been found in cancer patients who receive anti-angiogenic therapies (Ishak et al. 2014). In line with this, severe toxicities and high cost of the currently used anti-angiogenic drugs have urged an alternative approach. Scientists have concentrated on natural anti-angiogenic constituents from plants because these inexpensive molecules have a minimal or low toxicity, and were applied for centuries worldwide for the treatment in numerous diseases (Wang et al. 2015).

5.3.2 Anti-invasive and Anti-metastatic Agents

Matrix metalloproteinases (MMPs) were predominantly known for their roles in stimulating for cancer progression. MMPs exert its ability in degradation of connective tissue between the lining of blood vessels and the cells which promotes tumor

cells to metastasis (Gialeli et al. 2011). These data pave way for the development of broad-spectrum synthetic inhibitors to suppress MMP activity via interaction with Zn^{2+} ion in their active sites. Preclinical study showed that MMP inhibitors, for instance, batimastat (Davies et al. 1993), have a strong potential as anticancer agent (Gialeli et al. 2011). Batimastat, a hydroxamate derivative with poor water solubility, becomes the first MMP inhibitor evaluated in clinical trials (Macaulay et al. 1999). Batimastat has an ability to suppress several MMPs, such as MMP-1, MMP-2, MMP-7, and MMP-9, via binding to Zn^{2+} ions in the active site (Acharya et al. 2004). Compelling data has shown a promising antitumor activity of batimastat in in vivo studies on hemangioma, human ovarian cancer xenografts, mouse melanoma, and colon cancer (Watson et al. 1995; Eccles et al. 1996; Low et al. 1996). Hence, clinical studies of hydroxamate-based inhibitors were subsequently carried out (Mannello et al. 2005; Rao 2005; Vihinen et al. 2005), but the clinical data of these compounds were disappointing. From the study reviewed, marimastat was shown ineffective in a randomized phase III trial for metastatic breast cancer due to the musculoskeletal toxicity (Sparano et al. 2004).

In addition to the effects observed in hydroxamate-based inhibitors, non-hydroxamate MMP inhibitors were also used as MMP inhibitors such as rebimastat and thiol-based inhibitor SB-3CT. Rebimastat, known as BMS 275291, comprised of a thiol zinc-binding group and has been identified as a broad-spectrum MMP inhibitor. Rebimastat is a non-peptide mimetic, comprised of structural scaffold of the thiol in a deep-pocket binding, and had been shown to exert sheddase-sparing effect, thereby preventing suppression of metalloproteinases that promote the release of tumor necrosis factor (TNF), interleukin-1 (IL-1) receptor type 2, L-selectin, TNF receptor 2, and interleukin-6 (IL-6) receptor (Naglich et al. 2001). Surprisingly, a phase III trial in non-small cell lung carcinoma and a phase II trial in initial stage of breast cancer had shown an undesirable effect (Miller et al. 2004; Leighl et al. 2005).

In the past two decades, the MMP family has been tested in varieties of mammalian species, both at the protein and gene expression levels. Nearly 50 MMP inhibitors were evaluated in clinical study. Although promising preclinical data supported the MMP inhibitors as anticancer therapies, all phase III clinical trials have failed. From the studies reviewed, numerous MMP-coding genes have been knocked out in in vivo experiments, suggesting an in vivo model to study the consequences without presence of these genes. Of the study reported, MMPs are still considered as a crucial biological mediator which is implicated in many disorders. It is intriguing why, though their target ability, the development and marketing of these MMP inhibitors have been delayed so much (Vandenbroucke and Libert 2014).

While clinical studies with several MMP inhibitors are continuous, new research evidences concern about the role of MMPs which have yet to be fully defined, and the whole story turned out to be more complex than previously thought. This information suggests that all MMPs stimulate the development of cancer was a misconception, because not all MMPs have been recognized when the first clinical study was initiated. Thus, it provides evidences that not all MMPs need to be blocked at all times and in all cases (Iyer et al. 2012). Indeed, MMPs can have differential effects on tumor progression, depending on their substrates, for instance, angiogen-

esis, tumor growth and survival, invasion, and immune response mediation (Lopez-Otin et al. 2009; Decock et al. 2011; Hadler-Olsen et al. 2013). On the other hand, MMPs are also processing enzymes which selectively break several non-matrix targets, for example, clotting factors, cytokines, cell surface receptors, other proteinases, and chemokines (Vanlaere and Libert 2009) as well as tissue-remodeling enzymes.

Previous clinical study using broad-spectrum MMP inhibitors found that prolonged treatment results in an undesirable adverse effect, especially inflammation and musculoskeletal pain (Drummond et al. 1999; Skiles et al. 2004). However, this effect was reversible; thereby in the following trials, the concentration was decreased to prevent these inadvertent outcomes. Therefore, MMP inhibitor concentrations were usually shown insufficient to affect tumor biology, and thereby combination therapies were never considered. Unfortunately, two clinical trials using the MMP inhibitor tanomastat in pancreatic cancer and small-cell lung cancer were halted in the early beginning when the patients given the inhibitor exhibited significantly shorter survival compared than that of the patients given placebo (Coussens et al. 2002). These unexpected outcomes were more likely due to the broad-spectrum inhibition of MMPs and the cross-inhibition of a disintegrin and metalloproteinase (ADAM) family members and aggrecanases (ADAMs with thrombospondin motifs (ADAMTS) family members) (Edwards et al. 2008; Tan Ide et al. 2013). Nonetheless, most of the studies showed that MMP inhibitors exert a side effect; we believe that there is still hope in the suppression of MMP as a therapeutic strategy in the treatment of inflammatory-associated disorders. Therefore, natural product has played a central role in the development of significant number of drug candidate compounds.

5.4 Natural Compounds as Anticancer Agents

Natural compounds have been recognized as an excellent tool in evaluation of the molecular targets and act as therapeutic and chemopreventive compounds for biomedical applications (Kelkel et al. 2010; Schumacher et al. 2011a, b; Orlikova and Diederich 2012; Trecul et al. 2012).

Several studies have revealed that phytochemicals contained in natural products can suppress the initiation, promotion, and progression of carcinogenesis and some of their medicinal compounds hold a great promising chemopreventive and chemotherapeutic approach against cancers (Gupta et al. 2010; Lee 2010). Plants traditionally identified for the treatment of several cancer diseases (Orlikova and Diederich 2012) (Table 5.1) have seldom shown an association with the side effects compared with that of the modern chemotherapy (Jung Park and Pezzuto 2002). Realizing the potential benefits of plant-derived compounds as a source of active anticancer components, the National Cancer Institute (USA) studied nearly 35,000 plant products from 20 countries and has determined about 114,000 plant extracts for anticancer activity (Shoeb 2006). Out of the 92 anticancer drugs available prior to 1983 in the

Table 5.1 Plants with anticancer activity in vitro

Plant-derived compounds	Types of cancer cells	References
Procyanidins B1 and B2, (−)-epicatechin, (+)-catechin, phloretin, phloretin-2'-O-glycoside, quercetin, quercetin-3-O-glycoside, caffeic and chlorogenic acids	Colon cancer (Caco-2) cell line	Bellion et al. (2010)
Phloretin	Skin cancer cells	Funari et al. (2011)
Xanthone V1	Breast adenocarcinoma (MCF-7) and cervical carcinoma (HeLa and Caski)	Kuete et al. (2011)
2-Acetylfuro-1,4- naphthoquinone	Cervical carcinoma (HeLa and Caski), leukemia T-cells (PF-382), and skin melanoma (Colo38) cells	Kuete et al. (2011)
Artepillin C, quercetin, kaempferol, p-coumaric acid	Prostate cancer (LNCaP) cell line	Szliszka et al. (2011)
Cycloartane triterpenoid	Colon cancer (HT-29) cell line	Awang et al. (2012)
Daidzin, genistin, daidzein, genistein	Prostate cancer (LNCaP, C4-2B) cell line	Dong et al. (2012)
Cycloart-24-ene-26-ol-3-one	Colon cancer (HT-29) and (Caco-2) cells	Leong et al. (2016)

United States, 60% are of natural origin among the ones sold between 1983 and 1994 worldwide (Newman and Cragg 2012). About 80% of plant-derived molecules were associated with their original ethnopharmacological purposes (Tuorkey 2015; Swamy et al. 2016).

5.5 Plant-Derived Compounds Tested in Clinical Trials

Looking back the list of drugs approved in the last decades exhibits that plant-derived compounds are still vitally important in drug development. There are wealthy numbers of phytochemical studies describing new substances isolated from plants. Preclinical studies, which are in vitro, cell-based, and animal experiments on the mode of action in these substances, are available in an inconceivable quantity. However, these data are often of equivocal quality, particularly in the field of anti-inflammatory and anti-metastatic (Table 5.2) compounds. Further, literature review is overwhelming, and there are many comprehensive publications available on the respective underlying mode of action (Bellik et al. 2012; Sultana and Saify 2012; Leiherer et al. 2013; Orlikova et al. 2014). The knowledge on newly isolated components is often based on a very limited number of cell-based studies. From alterations of several key mediators of inflammatory processes, most often the transcription factor, nuclear factor-kappa B (NF-κB), the compound usually is evaluated to be an

Table 5.2 Anti-invasive and anti-metastatic properties of plant extracts or plant-derived compounds

Plant extracts or plant-derived compounds	Findings	Mechanisms	References
Glycyrrhiza uralensis	Inhibit cell migration and invasion of prostate cancer (DU145) cells	Downregulation of MMP-2 and MMP-9 and upregulation of TIMP-2	Park et al. (2010)
Chrysanthemum indicum	Suppressed proliferation and invasion of hepatocellular carcinoma (MHCC97H) cells	Downregulation of MMP-2 and MMP-9 expression and upregulation of TIMP-1 and TIMP-2	Wang et al. (2010)
Ipomoea obscura	Inhibits proliferation, invasion, migration, metastasis of melanoma (B16-F10) cells	Upregulation of TIMP, downregulation expression of inflammatory mediators via inhibition of NF-κB signaling, and inhibition of MMP-9 and MMP-2	Hamsa and Kuttan (2011)
Tripterygium wilfordii Hook F	Inhibited growth, migration, invasion, and metastasis of colon cancer (HT-29 and HCT116) cells	Downregulation of VEGF and COX-2, inhibition of cytokine receptor expression (CXCR4, TNFα, and TGF-β)	Johnson et al. (2011)
Annona muricata leaves	Effectively suppressed the migration and invasion of colon cancer (HCT-116 and HT-29) cells	Upregulation of Bax and downregulation of Bcl-2 proteins	Moghadamtousi et al. (2014)
Gypenosides	Inhibited cell proliferation and migration in colon cancer (SW620) and esophageal cancer (Eca-109) cells in dose- and time-dependent manners	Elevated intracellular ROS level and decreased the mitochondrial membrane potential	Yan et al. (2014)
Nuciferine, extracted from *Nelumbo nucifera Gaertn*	Inhibited the growth of non-small cell lung cancer (NSCLC) cells	Downregulation of β-catenin expression and its downstream targets such as c-myc, cyclin D, and VEGF-A and decreased the ratio of Bcl-2/Bax	Liu et al. (2015)
Solamargine	Inhibited migration and invasion of human hepatocellular carcinoma (HepG2) cells	Downregulation of MMP-2 and -9 expression	Sani et al. (2015)
Lupeol	Inhibited invasion of gallbladder carcinoma (GBC-SD) cells	Suppression of EGFR/MMP-9 signaling pathway	Liu et al. (2016)

(continued)

Table 5.2 (continued)

Plant extracts or plant-derived compounds	Findings	Mechanisms	References
Naringenin	Inhibited migration of lung cancer (A549) cells	Inhibition of Akt activities and reduction of MMP-2 and MMP-9 activities	Chang et al. (2017)
Enterolactone	Suppresses migration and invasion of lung cancer (A549 and H460) cell lines	Modulation of FAK-Src signaling pathway	Chikara et al. (2017)
Curcumin	Attenuates endometrial carcinoma cells migration	Slit-2 mediated downregulation of CXCR4, SDF-1, and MMP-2/MMP-9	Sirohi et al. (2017)

COX-2 cyclooxygenases-2, *CXCR-4* C-X-C chemokine receptor type 4, *EGFR* epidermal growth factor receptor, *FAK* focal adhesion kinase, *MMP* matrix metalloproteinases, *NF-κB* nuclear factor-kappa B, *ROS* reactive oxygen species, *SDF-1* stromal cell-derived factor 1, *TGF-β* transforming growth factor beta, *TIMP* TIMP metallopeptidase inhibitor, *TNFα* tumor necrosis factor alpha, *VEGF* vascular endothelial growth factor

anti-inflammatory without presenting a comprehensive in vivo study. Animal experiments are of course indispensible for the analysis of the pharmacological compound, but these models are insufficient and inconclusive, as commonly known, and do not satisfactorily reflect or show the exact condition in humans. Therefore, in the following sections, we will highlight the potential plant-derived anticancer agents that have been tested in humans, vinca alkaloids and its semisynthetic analogues, curcumin, colchicine, epigallocatechin-3-gallate (EGCG), betulinic acid, and podophyllotoxin derivatives. Chemical structures of plant-derived compounds tested in clinical trials and their sources are shown in Fig. 5.1.

5.5.1 Vinca Alkaloids and Its Semisynthetic Analogues

Compounds derived from plants play a critical role in the development of clinically useful anticancer agents. The first anticancer agents which precede into clinical trials were the vinca alkaloids, vincristine, and vinblastine from the Madagascar periwinkle, *Catharanthus roseus* (L.) (Apocynaceae), which were used as to treat testicular, lung, and breast cancers, lymphomas, leukemia, and Kaposi's sarcoma (Unnati et al. 2013). Another example is vinflunine, a dihydro-fluoro derivative of vinorelbine, which has been approved by the European Medical Agency (EMEA) in 2009 as the second-line chemotherapy in metastatic urothelial cancer (Bachner and De Santis 2008; Mamtani and Vaughn 2011). Vinflunine binds to the tubulin molecules, suppressing microtubule polymerization and the formation of tubulin paracrystals (Kruczynski et al. 1998; Bennouna et al. 2008). This binding

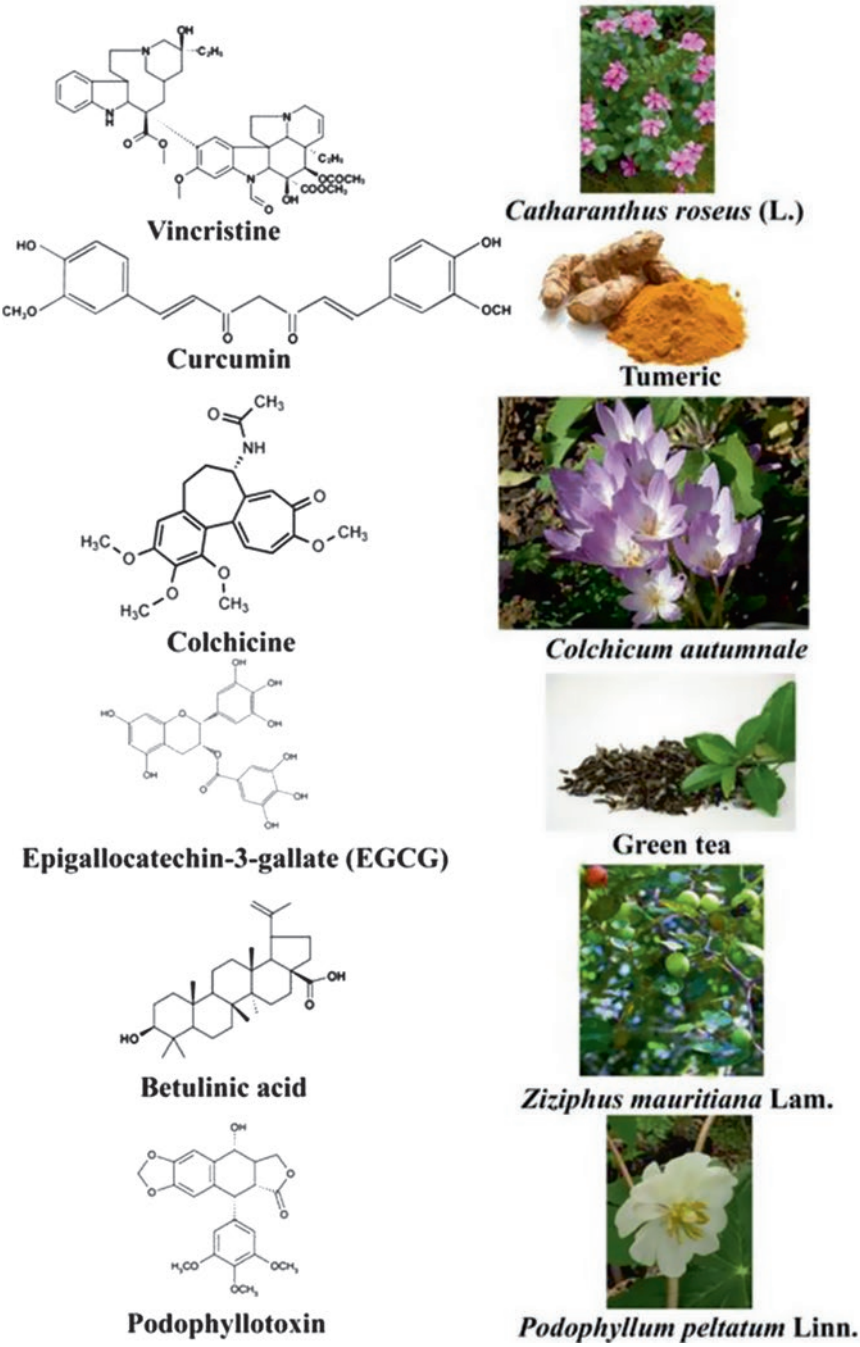

Fig. 5.1 Chemical structures of plant-derived compounds tested in clinical trials and their sources

subsequently causes the cell cycle arrest at G_2/M phase and induction of apoptosis (Kruczynski et al. 2002; Lobert and Puozzo 2008). Such results have been reported in both in vitro and in vivo studies against several types of malignant cell lines. Vinflunine is well studied in patients particularly non-small cell lung carcinoma and metastatic breast cancer in phase II/III clinical trials. Likewise, vinflunine is also being evaluated for its efficacy in advanced solid tumors in phase I/II trials (Ng 2011).

5.5.2 Curcumin

Curcumin, a polyphenol isolated from turmeric (*Curcuma longa*, Zingiberaceae), usually used as spices, exerts both anticancer and anti-inflammatory properties (Aggarwal et al. 2013; Naksuriya et al. 2014). With regard to its anti-inflammatory activity, curcumin was found to suppress predominant proinflammatory signaling cascades, including lipoxygenase (LOX), mitogen-activated protein kinase (MAPK), NF-κB, and COX pathways (Hong et al. 2004; Kim et al. 2005). Curcumin has also been reported to downregulate the secretion of prominent cytokines, for example, interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) (Shah et al. 2010). Furthermore, curcumin also blocks the expression of cell adhesion molecules, like intercellular adhesion molecule-1 (ICAM-1), which is needed for the binding of leukocytes with endothelial cells (Kumar et al. 1998). In addition, curcumin was also shown to suppress basic fibroblast growth factor (bFGF) (1 ng/mL)-induced endothelial cell proliferation in a dose-dependent manner (Arbiser et al. 1998). They concluded that 10 mg of curcumin can suppress bFGF (80 ng)-mediated corneal neovascularization in mice; however, no effect was observed in phorbol ester-stimulated *vascular endothelial growth factor* (*VEGF*) mRNA production. Treatment with 1 mM of hydrazinocurcumin-encapsulated nanoparticle in RAW264.7 macrophages causes induction of polarization of macrophages from M2 to M1 phenotype via suppression of signal transducer and activator of transcription 3 (STAT 3) (Zhang et al. 2013). In contrast, 25 μmol/L of curcumin had shown a stimulation of polarization in RAW264.7 cells into M2 phenotype via secretion of interleukin-4 (IL-4) or interleukin-13 (IL-13) and promotion of proliferator-activated receptor gamma (Chen et al. 2014; Gao et al. 2015).

Interestingly, curcumin not only present a promising anti-inflammatory profile, but also exhibit as a potential pleiotropic compound with different mechanisms of action. The clinical trial list of curcumin is explained in more detail in Gupta et al. (2013). In a study, curcumin served as an adjunct therapy or as a dietary supplement. It should be noted that bioavailability of curcumin is very low, despite continuous efforts which have been made to overcome this obstacle using chemical and technological approaches (Anand et al. 2007). Curcumin becomes an approved alternative for the prevention or treatment in one of the mentioned indications. However, it requires more studies in the future for real applicability. Taken

together, from the mounting of research evidences, it can be concluded that curcumin seems to exert a good safety with well-tolerated and nontoxicity profiles.

5.5.3 *Colchicine*

The tropolone derivative colchicine is a major alkaloid found in the plant *Colchicum autumnale* (Colchicaceae), also known as meadow saffron or autumn crocus. This plant extract has been used in gout attacks since ancient times ago. Surprisingly, the United States Food and Drug Administration (FDA) have approved colchicine for the prevention and treatment of acute gout flares as well as treatment of familial Mediterranean fever. The underlying mechanism of colchicine is well evaluated with the molecular targeting in tubulin, the binding site was characterized accurately, and the biological consequences of impairing microtubule dynamics were investigated (Bhattacharyya et al. 2008; Stanton et al. 2011). Colchicine was shown not only as a microtubule destabilizer, which exerts a strong binding capacity to tubulin (Stanton et al. 2011; Lu et al. 2012; Sivakumar 2013), but it increased cellular free tubulin to control mitochondrial metabolism in cancer cells via suppression of voltage-dependent anion channels in the mitochondrial membrane (Maldonado et al. 2010). Previous study revealed that clinically acceptable colchicine doses, in a range of 2–6 ng/mL, had a potential in the palliative treatment of cholangiocarcinoma (Wu et al. 2015) and hepatocellular carcinoma (Lin et al. 2013). These findings are further supported by another study, which observed that administration of colchicine inhibited the proliferation of human gastric cancer (AGS and NCI-N87) cell lines (Lin et al. 2016).

A wide ranging information has shown that colchicine is being approved as a drug. However, investigators are continued to conduct clinical studies to gain a better understanding in this field of application. An emerging study has been conducted using colchicine as an adjunct treatment towards inflammation-associated pathologies, including acute (Imazio et al. 2013), recurrent pericarditis (Imazio et al. 2011), and the results showed positive outcomes, including prevention of atrial fibrillation after radio-frequency ablation (Deftereos et al. 2012) and postpericardiotomy syndrome (Imazio et al. 2010). These large and well-performed investigations will definitely influence pharmacotherapy guidelines. However, due to a large number of diseases associated with inflammation, colchicine is worth for understanding further.

5.5.4 *Epigallocatechin-3-Gallate*

Epigallocatechin-3-gallate (EGCG) is a predominant bioactive constituent of green tea, *Camellia sinensis* (Theaceae). EGCG is the primary component of the green tea catechins and accounts for 50–80% of all catechins in a cup of green tea (Singh et al. 2011). EGCG has been reported to have anti-inflammatory, antioxidant,

anti-infective, anticancer, anti-angiogenetic, and chemopreventive activities (Domingo et al. 2010; Singh et al. 2011; Yang et al. 2011a; Riegsecker et al. 2013; Steinmann et al. 2013). The underlying mode of actions is also extremely large. EGCG stimulates cell cycle arrest and induces apoptosis via suppression of NF-κB and regulatory proteins in the cell cycle (Yang et al. 2011a). Moreover, it suppresses growth factor-dependent signaling, including epidermal growth factor (EGF), VEGF, and insulin-like growth factor-I (IGF-I), the MAPK pathway, COX-2 expression, and proteasome-dependent degradation (Yang et al. 2011b). Masuda et al. (2011) however reported that EGCG may modify the growth factor receptor signaling. Moreover, EGCG suppresses topoisomerase II, DNA methyltransferase 1, and telomerase, thus altering the chromatin functions (Bandele and Osheroff 2008). Unfortunately, promising preclinical data and the thorough mechanistic action, clinical research evidences conducted in the field of inflammation are insufficient. Research findings found that a beneficial effect of topical EGCG treatment against acne vulgaris in clinical trials, and is speculated due to anti-inflammatory properties of EGCG (Yoon et al. 2013), suggesting that EGCG could lessen inflammatory changes. This improvement fuelled future research to explore EGCG indications. Furthermore, a study reported by Furst and Zundorf (2014) has shown that EGCG will also be evaluated for multiple system atrophy, diabetic nephropathy, muscular dystrophy of the Duchenne type, patients with cardiac amyloid light-chain amyloidosis, fragile X syndrome, Huntington's disease, early stage of Alzheimer's disease, and Down syndrome. In addition, trials will be conducted to investigate the potential of EGCG in patients with Epstein-Barr virus and high risk for recurrent colon adenoma. Taken together, it is more likely that EGCG will expand its indication in the future, suggesting EGCG might exert enormous functional potentials.

5.5.5 Betulinic Acid

Betulinic acid is a pentacyclic triterpenoid with a lupane skeleton, isolated from *Ziziphus mauritiana* Lam. (Rhamnaceae) (Pisha et al. 1995). Triterpenoid has been demonstrated to cause cytotoxicity against brain tumor and neuroectodermal cells (Zuco et al. 2002). This finding was further confirmed by the evaluation of betulinic acid in in vivo selective proliferation inhibitory activity in athymic mice bearing human melanoma xenografts (Pisha et al. 1995). The fact that betulinic acid inducing cytotoxicity is by causing apoptosis via modulation of the intrinsic pathway as evaluated using mitochondrial membrane potential and stimulation of p38 MAPK and stress-activated protein/c-Jun N-terminal kinase (SAP/JNK) initiated by reactive oxygen species (ROS) (Laszczyk 2009). Accordingly, a betulinic acid-containing ointment was conducted in phase I/II clinical trials for the treatment of dysplastic nevi with a moderate to severe dysplasia (NIH 2010).

5.5.6 *Podophyllotoxin Derivatives*

Podophyllotoxin and deoxypodophyllotoxin have been identified as naturally occurring aryltetralin lignans (Srivastava et al. 2005). The Podophyllaceae family species including *Podophyllum peltatum* Linn. and *Podophyllum emodii* Wallich. have been recognized in the treatment of warts and skin cancer. It is also effective in the treatment of non-Hodgkin's lymphoma, lung cancer, other lymphomas, genital tumors, and Wilms' tumors (Utsugi et al. 1996; Subrahmanyam et al. 1998). The interest was also expanded to an alcohol extract of its dried roots containing podophyllin which was effective against venereal warts when applied topically. Other associated podophyllotoxin compounds including lignans were purified and introduced into clinical trials, but unfortunately it was halted due to the undesirable toxicity. Mounting research evidences conducted between the 1960s and 1970s at Sandoz Laboratories in Switzerland led to the development of teniposide and etoposide as clinical agents which are being used in the treatment of bronchial, testicular, and lymphatic cancers. Among 2069 anticancer clinical trials recorded by the National Cancer Institute (NCI) since July 2004, more than 150 are drug combinations such as etoposide toward numerous of cancers (Lee and Xiao 2005).

5.6 Mechanisms of Action of Plant-Derived Compounds as Anticancer Agent

A summary of studies on mechanisms of anticancer activity of plant-derived compounds is shown in Tables 5.2 and 5.3. Plant-derived compounds present naturally in plants may be beneficial in the amelioration of oxidative stress (Shah et al. 2010; Yoon et al. 2013). Therefore, we will focus the involving mechanisms in plant-derived compounds in the modulation of cell proliferation, inflammation, and angiogenesis.

5.6.1 *Apoptosis Induction and Inhibition of Cancer Cellular Proliferation*

Polyphenols are members of chemical constituents, present in a variety of plants and fruits, like curcumin in *Curcuma longa*, resveratrol in berries and grapes, and catechins from tea (Manach et al. 2004). These bioactive compounds show an antiproliferative effect against tumor-associated stromal cells and tumor cells, such as endothelial cells, and inhibit tumorigenesis via modulation of anti-angiogenic, antiproliferative, and antioxidant activities (Wang et al. 2015).

Table 5.3 Anti-angiogenic properties of plant extracts or plant-derived compounds

Plant extracts or plant-derived compounds	Findings	Mechanisms	References
Patrinia villosa Juss	Inhibition HUVECs proliferation, migration, and formation of tubelike structures	Induction of FAK and Akt phosphorylation	Jeon et al. (2010)
Cinnamon	Inhibition of VEGF-induced proliferation, migration, and formation of tubelike structures	Suppressed VEGFR2 kinase activity, MAPK, and STAT3 signaling	Lu et al. (2010b)
Allium ascalonicum	Inhibition sprouting and capillary tube formation in HUVECs	N.E.	Seyfi et al. (2010)
Triphala churna	100 mg/kg on matrigel assay, 40 μg/mL on CAM assay, and 40 μg/mL on HUVECs	Phosphorylation of VEGFR2	Lu et al. (2012)
Pithecellobium jiringa (Jack) Prain	Inhibition of other angiogenesis cascades including migration of endothelial cells and formation of capillary network on matrigel matrix	Arrested the growth of human endothelial cells via downregulation of VEGF expression	Muslim et al. (2012)
Catechin derivatives	1.5 mg of EGCG on HT-29 xenografts, 10 mg/kg of EGCG on 4 T1 breast cancer xenografts, 40 mg/L EGCG on MDA-MB231 cells, 30 μM EGCG on HT29 cells, and 0.75–25 μM EGCG on neutrophils	Protein kinase C, c-fos and c-Jun, STAT3, NF-κB, Erk-1/2 phosphorylation, TAM infiltration and polarization, and neutrophil migration	Jang et al. (2013)
Brucine from *Strychnos nux-vomica*	20 or 40 μM on rat aortic ring assay, 10 mg/kg on matrigel assay, and EAC tumor xenografts 5–40 μM on HUVECs	Src, FAK, Erk, Akt, and mTOR phosphorylation, VEGF, and NO production	Saraswati and Agrawal (2013)
Tylophorine from *Tylophora indica*	7.5 mg/kg on EAC tumor xenografts 2.5–20 μM on HUVECs	PI3K/Akt/mTOR signaling	Saraswati et al. (2013)
Deguelin	Treatment of deguelin showed anti-angiogenesis against cancer	Inhibition of HIF-1α-VEGF pathway	Wang et al. (2013)
Nicotiana glauca, *Tephrosia apollinea*, *Combretum hartmannianum*, and *Tamarix nilotica*	Exhibited remarkable anti-angiogenic activity	Inhibiting the sprouting of microvessels more than 60%	Hassan et al. (2014)

(continued)

Table 5.3 (continued)

Plant extracts or plant-derived compounds	Findings	Mechanisms	References
Resveratrol	5.7 μg/mL on T241 fibrosarcoma xenografts, 1.5 mg/kg of HS-1793 on FM3A breast cancer xenografts	Akt, MAPK phosphorylation, S6 protein, HIF-1α expression, secretion of IFN-γ and programming of TAM	Jeong et al. (2014)
	50 μM on A2780/CP70 and OVCAR-3 cells		
Curcumin	3000 mg/kg on HepG2 xenografts, 10 mg on mouse corneal	VEGF production, STAT3, proliferator-activated receptor gamma, IL-4 and IL-13 production, and TAM polarization	Gao et al. (2015)
	0.5–10 μM on primary endothelial cells, 1 mM of hydrazinocurcumin-encapsulated nanoparticles on RAW264.7 macrophages, and 25 μmol/L of curcumin on macrophages		
Gallic acid	Possess anti-angiogenesis against ovarian cancer	Inhibited VEGF secretion and suppressed in vitro angiogenesis in a dose-dependent manner	He et al. (2016)
Galium aparine	Inhibited the angiogenesis in MCF-7 and MDA-MB-231 cells	Decreased proangiogenic cytokines such as NRG1-β1, VEGF, and TF	Atmaca (2017)
Acorus calamus extracts	Inhibited the angiogenesis in HUVEC cells	Downregulation of Oct4 and nucleostemin	Haghighi et al. (2017)

CAM chick chorioallantoic membrane, *EAC* esophageal adenocarcinoma, *EGCG* epigallocatechin-3-gallate, *Erk* extracellular signal-regulated kinase, *FAK focal adhesion kinase*, *HepG2* human liver cancer cell line, *HIF-1α* hypoxia-inducible factor-*1* alpha, *HIF-1α-VEGF* hypoxia-inducible factor-*1* alpha-vascular endothelial growth factor, *IFN-γ* interferon gamma, *IL* interleukin, *MAPK* mitogen-activated protein kinases, *MCF-7* and *MDA-MB-231* human breast cancer, *mTOR* mammalian target of rapamycin, *NE* not elucidated, *NF-κB* nuclear factor-kappa B, *NO* nitric oxide, *NRG1* neuregulin-1, *A2780/CP70* and *OVCAR-3* ovarian cancer cell lines, *PI3K* phosphoinositide 3-kinase, *STAT3* signal transducer and activator of transcription 3, *TAM* tumor-associated macrophages, *TF* tissue factor, *VEGF* vascular endothelial growth factor, *VEGFR2* vascular endothelial growth factor receptor 2

Apoptosis is a complex process that contributes to programmed cell death involving the mitochondria (the intrinsic pathway) or the stimulation of death receptors (the extrinsic pathway). These intrinsic and extrinsic pathways cause the stimulation of caspases, including effector caspases (caspase-3, caspase-6, and caspase-7) and initiator caspases (caspase-2, caspase-8, caspase-9, and caspase-10). These two pathways then converge to activate caspase-3, which subsequently induce apoptosis (Thornberry and Lazebnik 1998). Oxidative stress and DNA damage are common signals that stimulate the mitochondrial apoptotic pathway and contribute to cyto-

chrome C release and mitochondrial membrane rupture (Thornberry 1998; Thornberry and Lazebnik 1998).

Research evidences have revealed that the anticancer ability of some dietary polyphenols, like luteolin, quercetin, apigenin, resveratrol, and genistein, may contribute to the induction of apoptosis in in vitro and in vivo studies (Gopalakrishnan and Tony Kong 2008; Surh 2008; Vauzour et al. 2010). In line with this, the apoptosis-inducing activity of EGCG has also been demonstrated to upregulate Fas expression and caspase-3, caspase-8, and caspase-9 in several cancer cell lines (Kawai et al. 2005; Nishikawa et al. 2006), as well as inhibition of BH3-interacting domain death agonist, apoptosis-suppressing proteins, B-cell lymphoma (Bcl)-2, and Bcl-extra large (Bcl-xL) (Lee et al. 2004; Nishikawa et al. 2006). Also, an earlier study found that genistein caused inhibition of breast cancer cells in a concentration and time-dependent manners with no harm toward normal breast epithelial (MCF10A) cells (Ullah et al. 2011). This is due to normal breast epithelial cells which exert no detectable copper (Daniel et al. 2005), which may partially explain their resistance observed in polyphenol-induced proliferation. The DNA damage induced by polyphenols in lymphocytes is modulated by the ROS generation. Accordingly, the anticancer activity present in the polyphenolic compounds has the potential to modulate prooxidant pathway, subsequently leading to cell death. A similar effect was also observed in resveratrol, which behave as prooxidative agents in human cancer cells (Santandreu et al. 2011). Likewise, results toward the same direction were presented by Shamim et al. (2012), who reported that polyphenol-induced apoptosis and DNA breakage in peripheral lymphocytes of pancreatic cancer at acidic pH. Overall, these data suggest that epithelial tumors have lower pH than that of normal tissues due to a high rate of glycolysis, lack of hypoxia, and vasculature, followed by lactate fermentation (Gerweck and Seetharaman 1996).

5.6.1.1 Pinocembrin

Pinocembrin has been found in numerous plants including the genera of *Piperaceae* family, which consists of 1950 species and 14 genera. Pinocembrin is a flavonoid compound derived from vegetables, fruits, seeds, nuts, spices, stems, flowers, herbs, red wine, and tea (Fig. 5.2) (Jiang and Morgan 2004; Miyahisa et al. 2006). Pinocembrin contained numerous pharmacological properties associated with inflammation by suppressing of vascular ailments, cancer growth, and bacterial colonization (Manthey et al. 2001; Touil et al. 2009). Pinocembrin found in the root of *Alpinia pricei* and *Alpinia galangal* has also been reported to exert anti-inflammatory (Hsu et al. 2010; Yu et al. 2009) and anticancer properties (Kumar et al. 2007). Furthermore, pinocembrin is also cytotoxic toward colon cancer (HCT-116) cells, with no harm against human umbilical cord endothelial cells (Kumar et al. 2007). From the study reviewed, pinocembrin activated caspase-3 and caspase-9 and mitochondrial membrane potential (MMP) activity in HCT-116 cell line (Kumar et al. 2007; Punvittayagul et al. 2011). In vivo and in vitro studies also found that pinocembrin can enhance the biological functions in medium-term

carcinogenicity and liver micronucleus in rats. This observed effect suggests that pinocembrin may protect against chemical-induced hepatocarcinogenesis (Punvittayagul et al. 2012).

5.6.1.2 Allicin

Allicin, also known as diallylthiosulfinate, is a sulfur-containing natural constituent in garlic (*Allium sativum* L.) (Fig. 5.2). Sulfur-containing components in onion and garlic are predominantly from the precursors of S-alk(en)yl-L-cysteine sulfoxides (ASCOs) and γ-glutamyl-S-alk(en)yl-L-cysteines (Kubec et al. 1999). Allicin exerts strong antimicrobial properties and thus potentially acts as a potent antibiotic in vitro (Borlinghaus et al. 2014). Furthermore, mounting evidence also indicates that allicin induces apoptosis and resulted in a redox shift in human leukemic cell lines (Miron et al. 2008). This activity subsequently resulted in the execution of cell death, both in caspase-independent (Park et al. 2005) and caspase-dependent (Oommen et al. 2004) pathways. Chu et al. (2013) had demonstrated that allicin enhanced p53-mediated autophagic cell death in hepatocellular carcinoma. The antiproliferative effect was not only shown in human leukemic and hepatocellular carcinoma cell lines, it also further induced apoptosis via mitogen-activated protein kinases/extracellular signal-regulated kinase (MAPK/ERK) and bcl-2/bax mitochondrial pathways in glioblastoma (Cha et al. 2012). Likewise, allicin also suppressed proliferation and induced apoptosis via p38 MAPK/caspase-3 signaling pathways in gastric cancer (Zhang et al. 2015). Moreover, allicin improved hypodiploid DNA content and enhanced releasing of cytochrome C from mitochondria

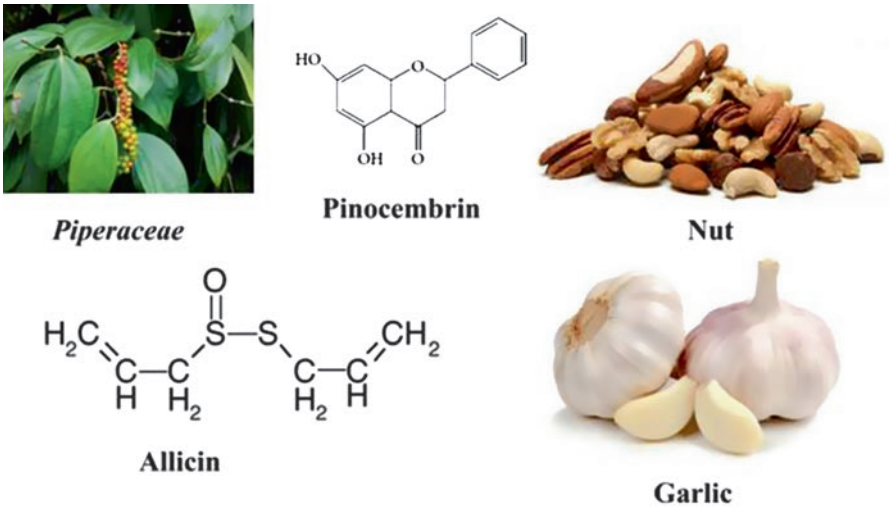

Fig. 5.2 Chemical structures of plant-derived compounds and their sources induced apoptosis and inhibited cancer cell proliferation

to cytosol capability and subsequently contributed to apoptotic colon cancer cell death (Bat-Chen et al. 2010). Additionally, the inhibition of cancer cells induced by allicin is also modulated by apoptosis-inducing factor (AIF). Of the study reported, nuclear factor E2-related factor 2 (Nrf2) is often described as an anti-apoptotic factor in the regulation of Bcl-2 and Bcl-xL expression (Niture and Jaiswal 2012; Niture and Jaiswal 2013).

5.6.2 Interfering with Inflammatory Signaling

Despite the type of inflammatory responses which may differ between diseases, inflammation and disease conditions are associated via production of inflammatory mediators by neutrophils and macrophages. COX-1 and COX-2 overexpressions produce inflammatory mediators like prostaglandin E 2 (PGE 2). Anti-inflammatory drugs with combination of nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the inflammatory response through inhibition of infiltration and stimulation of inflammatory cells and release of mediators or inflammatory mediators (Urban 2000).

Numerous compounds mediate the COX-2 expression by modulation of MAPK signaling pathways. Indeed, p38 and ERK phosphorylation can be suppressed by curcumin (Yu and Shah 2007), resveratrol (Kundu et al. 2004), and epigallocatechin-3-gallate (EGCG) (Peng et al. 2006). Furthermore, c-Jun N-terminal kinase (JNK) stimulates the transcription factor of activator protein-1 (AP-1), which is suppressed by diallyl polysulfides from onion and garlic (Shrotriya et al. 2010). The suppression of the MAPK signaling prevents stimulations and nuclear translocation of transcription factors that interact with the specific sites of the promoter of COX-2 and ultimately suppressed the COX-2 expression. In addition to the effects observed in curcumin, resveratrol, EGCG, and diallyl polysulfides, apigenin, a flavone isolated from chamomile, has also been shown to have a similar effect against NF-κB activity. It was demonstrated to suppress IκB kinase (IKK), which resulted in inhibitory subunit of nuclear factor-kappa B alpha (IκBα) phosphorylation. IκBα sequesters NF-κB and prevents its translocation into the nucleus and the binding with its subunits (p65 and p50) and the promoter. AP-1 comprised of c-Fos and c-jun subunits has been demonstrated to suppress by curcumin in endometrium carcinoma. Similarly, this factor is also suppressed by diallyl trisulfides (Shrotriya et al. 2010), quercetin (Crespo et al. 2008), and resveratrol in non-carcinogenic mammary epithelial cells (Kundu et al. 2006).

5.6.2.1 Capsaicin

Capsaicin, a hydrophobic alkaloid derived from chili peppers (*Capsicum* species, Solanaceae), (Fig. 5.3) is recognized for its typical spiciness in the genus *Capsicum*. Capsaicin has been traditionally used as a counterirritant and topical rubefacient to

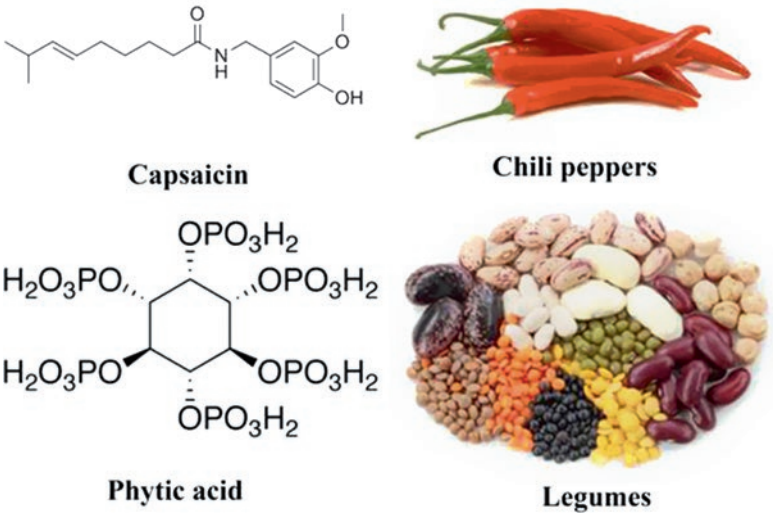

Fig. 5.3 Chemical structures of plant-derived compounds and their sources modulate inflammation

ameliorate joint and muscle pains. Capsaicin has been reported to suppress ethanol-induced gastric mucosa inflammation in rats (Park et al. 2000) and paw inflammation in arthritic rats (Joe et al. 1997). Furthermore, capsaicin has also been demonstrated to suppress inducible nitric oxide synthase (iNOS), NF-κB, and COX-2 expression in macrophages in a transient receptor potential channel vanilloid subfamily member 1 (TRPV1)-independent way (Kim et al. 2003). TRPV1 is a nonselective cation channel which has a high preference of Ca^{2+} and is primarily found in nociceptive neurons. It is often stimulated by physical and chemical stimuli, like low pH, inflammatory mediators, and heat (O'Neill et al. 2012).

5.6.2.2 Phytic Acid

Phytic acid is found predominantly in legumes, oilseed, and cereals (Fig. 5.3) (Schlemmer et al. 2009). Previous studies had demonstrated that phytic acid exerts numerous chemopreventive properties, such as anticancer and antioxidant properties (Norhaizan et al. 2011). Accordingly, phytic acid has been identified as a potential protective agent against cancer (Matejuk and Shamsuddin 2010). It inhibited different cancer cell proliferations via NF-κB activity (Agarwal et al. 2003; Kolappaswamy et al. 2009) and COX-2 pathway (Shafie et al. 2013). NF-κB is a crucial factor found in epithelial-mesenchymal transition (EMT) and survival pathways. Thus, targeting NF-κB is deemed as a promising strategy in the treatment of cancer. Research evidence shows that phytic acid inhibited the proliferation of prostate carcinoma (Kapral et al. 2008) and prevents nuclear translocation in HeLa cells and luciferase transcription activity (Ferry et al. 2002). Additionally, phytic acid

also inhibited colon cancer (Caco-2) cells through modulation of NF-κB by blocking of the p65 subunit of NF-κB and its inhibitor IκBα (Schröterová et al. 2010).

5.6.3 Modulation of Angiogenesis Signaling Pathway

Angiogenesis is the sprouting of new blood vessels from pre-existing vessels and resulted in several pathological diseases including rheumatoid arthritis, proliferative retinopathies, solid tumorigenesis, and obesity (Folkman 1990). Tumor angiogenesis is implicated by an angiogenic imbalance, where proangiogenic factors predominate over anti-angiogenic factors. Additionally, angiogenesis also causes metastasis and growth of malignant tumors. Vascular endothelial growth factor-A (VEGF-A) has been identified as a critical angiogenic mitogen (Folkman 2002). Accordingly, tumor angiogenesis is considered as a vital pharmacological target in cancer prevention and treatment (Scappaticci 2003; Dell'Eva et al. 2004). Therefore, this hypothesis has prompted in the development of the angiotherapy. Anti-angiogenic strategy can overcome the undesirable outcomes and chemoresistance resulted from the chemotherapies. Anti-angiogenic drugs targeting sprouting of new blood vessels that provide tumors with oxygen, nutrients, and blood ultimately may block the tumor proliferation and metastasis.

Avastin is a monoclonal antibody for VEGF and fluorouracil-based combination therapy. It has demonstrated an improvement in survival of metastatic colorectal carcinoma patients (Hurwitz et al. 2004). On the other hand, conventional anti-angiogenic compounds based on monoclonal antibody technology may have a limitation in terms of cost. Therefore, plant with anti-angiogenic compounds is of great demands because they are inexpensive and can produce in huge quantities (Al-Suede et al. 2012).

Plants which have various phytochemical compounds are potential natural antioxidants, including flavonoids, polyphenolic acids, phenolic diterpenes, and tannins, (Dawidowicz et al. 2006) which exert a variety of biological activities. As shown in Table 5.3, a number of plant-derived compounds have demonstrated to exert anti-angiogenic properties via modulation of several signaling pathways. These plant-derived compounds primarily contain phytochemicals which may have prominent physiological activity in the body (Liu 2003). These bioactive constituents play an essential role as antioxidants, mimic hormones, interfere with DNA replication, stimulate enzyme activities, or bind to cell walls. Compelling data have described the synergistic activity of plant-derived compounds as anti-angiogenic agents with other antineoplastic drugs (Wang et al. 2007; Sak 2012).

5.6.3.1 Resveratrol

Resveratrol, a polyphenol naturally found in berries, grapes, and other plant sources (Fig. 5.4), modulates tumor angiogenesis through several molecular pathways (Cao et al. 2004; Wang et al. 2015). In vitro studies found that resveratrol can significantly suppress VEGF expression in human ovarian cancer cells (A2780/CP70 and

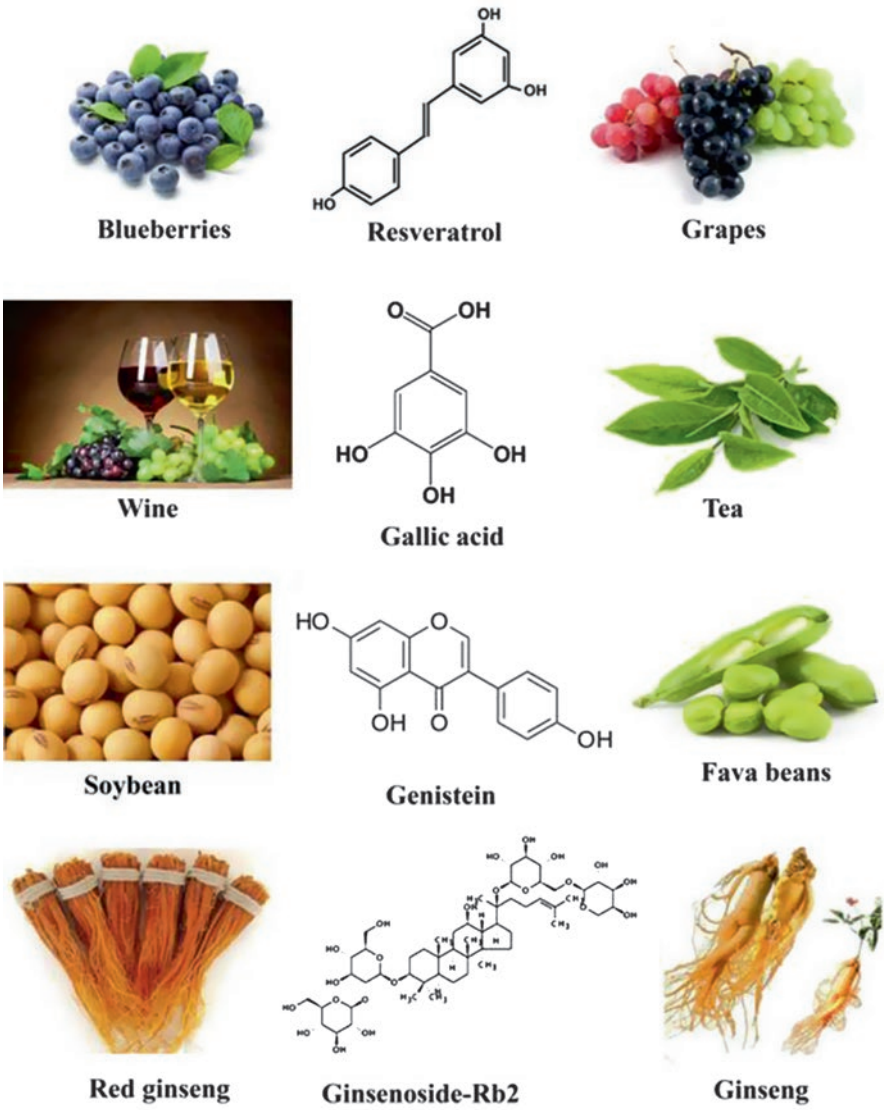

Fig. 5.4 Chemical structures of plant-derived compounds and their sources mediated angiogenesis

OVCAR-3) (Cao et al. 2004). A similar trend was also observed in in vivo study. Feeding T241 murine fibrosarcoma-bearing C57BL6 mice with 5.7 μg/mL of resveratrol has shown to suppress tumor growth via inhibition of new blood vessel formation and endothelial cell migration. In general, inhibition of cell migration was mediated through modulation of fibroblast growth factor 2 (FGF2) and vascular endothelial growth factor (VEGF) receptor-mediated stimulation of MAPK in endothelial cells (Brakenhielm et al. 2001). Moreover, resveratrol also modulates its activities via suppression of Akt- and MAPK-driven basal and insulin-like growth factor 1 (IGF-1)-mediated hypoxia-inducible factor 1 alpha (HIF-1α) expression as well as activation of proteasomal degradation of HIF-1 alpha (Cao et al. 2004).

5.6.3.2 Gallic Acid

Gallic acid is a polyphenol found primarily in berries, tea, wine, and grapes (Fig. 5.4). Gallic acid has demonstrated different biological and pharmacological properties, like antiviral, antitumor, and antibacterial activities in several human cancer cell lines including oral (Kuo et al. 2014), glioma (Lu et al. 2010a), lung (You et al. 2011), cervical (Zhao and Hu 2013), and pancreatic (Cedó et al. 2014) cancer cells. He et al. (2016) showed that gallic acid suppressed VEGF secretion and in vitro angiogenesis by HUVECs induced by the culture medium of ovarian cancer cell lines, OVCAR-3 and A2780/CP70, treated with different concentrations of gallic acid. In this study, He et al. (2016) further showed that gallic acid suppressed VEGF production via downregulation of hypoxia-inducible factor-1 alpha (HIF-1α). Hassan et al. (2014) further demonstrated that plants that are enriched with phenolic contents show a higher bio-efficacy compared than that of other plants, which adds reassuring weight to accumulating evidence showing that naturally phenolics are able to reduce the ROS in biological system. Oxidative stress generated by ROS plays a crucial role in the pathology-associated chronic disease including excessive vascularization and cancer (Kampa et al. 2007). ROS-induced cancer was shown in animal models which involved a multiple malignant transformation due to an alteration of gene expression and DNA mutations via epigenetic mechanisms and subsequently resulted an uncontrolled proliferation of cancerous cells. High expressions of ROS are usually seen in several cancerous cells (Irani et al. 1997; Yasuda et al. 1999; Yeldandi et al. 2000), and thereby suggest that ROS acts as a significant molecule in various growth-associated responses and ultimately promote tumorigenesis and angiogenesis (Ushio-Fukai and Nakamura 2008).

5.6.3.3 Flavonoids

Flavonoids, such as flavonols, flavones, flavanones, isoflavones, and anthocyanins, exhibit anti-angiogenic properties (Fotsis et al. 1997). Genistein, an isoflavonoid isolated from *Genista tinctoria* (Fig. 5.4), can suppress bFGF-mediated endothelial cell tube formation in vitro at a dosage of 150 μM by inhibition of plasminogen

activator (PA) and PA inhibitor-1 (Fotsis et al. 1993). Likewise, a low dosage of genistein (30 μM) has also been demonstrated to suppress bFGF of endothelial cells (Koroma and de Juan 1994). Other examples of plant-derived compounds are silibinin and silymarin, from the seeds and fruits of *Silybum marianum* (milk thistle), which also can suppress angiogenesis (Jiang et al. 2000; Singh et al. 2003). Feeding A/J mice with diet containing 742 mg/kg of silibinin prior to urethane administration demonstrated to inhibit growth and incidence of lung adenocarcinoma by a significant reduction in numbers of tumor-associated macrophages (Tyagi et al. 2009). Collectively, these data showed that numerous health benefits of flavonoids are attributed to their ability to act as an antioxidant.

5.6.3.4 Terpenoids and Tannins

Ginsenosides, such as ginsenoside-Rb2 and ginsenoside-Rg3, are usually isolated from the roots of red ginseng (*Panax ginseng*) (Fig. 5.4). These compounds have an ability to reduce the neovessels in murine B16 melanomas at an intravenous concentration of 10 μg or oral dosage of 100–1000 μg per mouse (Sato et al. 1994; Mochizuki et al. 1995). Nevertheless, another study also revealed that a mixture of saponins from ginseng at a dosage between 10 and 100 μg/mL may activate proliferation, endothelial cell migration, and tube formation (Morisaki et al. 1995). Besides ginsenosides, taxol is another plant-derived compound which modulates the angiogenesis. Taxol is a complex polyoxygenated diterpene derived from the bark of the Pacific yew tree (*Taxus brevifolia*). It destroys malignant tumor cells by disrupting their microtubule cytoskeleton (Foa et al. 1994) and hence demonstrates anti-angiogenic properties via inhibition of VEGF production and HIF-1α expression (Foa et al. 1994; Escuin et al. 2005).

Anti-angiogenic agent may target the endothelial cells or cancer at any necessary steps for neovascularization or carcinogenesis, including tube formation, differentiation, proliferation, or migration (Folkman 2003). Angiogenesis inhibitors may act by activating apoptosis in cells. Both in vitro experiments and in vivo models have indicated that many endogenous anti-angiogenic components may induce cytotoxicity via apoptosis (Tiwari 2012).

5.7 Effectiveness of Combined Standard Drug and Plant-Derived Compounds

Drug resistance is the primary factor that limits the chemotherapy application for cancer diseases (Waghray et al. 2015). Comparing to other monotherapy, 5-fluorouracil (5-FU) is more acceptable because sufficient concentrations usually can be administered in jaundice or hepatic dysfunction (Roderburg et al. 2011). Despite the low response rate of 5-FU monotherapy, given in combination to other

compounds, the response rates were increased until 28% (Roderburg et al. 2011). FOLFOX (5-FU, oxaliplatin, and leucovorin) regimen was reported to have a better disease control rate, higher median survival in hepatocellular carcinoma patients, and better objective response rate (Zhang et al. 2011). Therefore, administrations with combined 5-FU and other agents play a vital role in advanced hepatocellular carcinoma therapies.

Induction of apoptosis by chemotherapy drug is a complicated process, which is modulated via several signaling pathways and regulated by vast varieties of apoptosis-associated proteins (Das et al. 2010). The synergistic effect is observed in allicin and 5-FU in the induction of hepatocellular carcinoma cell death via ROS-mediated mitochondrial pathway, suggesting the therapeutic effect of allicin in hepatocellular carcinoma chemotherapy (Zou et al. 2016). From the study reviewed, allicin sensitized hepatocellular carcinoma cells to 5-FU-induced apoptosis via modulation of ROS mitochondrial pathway. In general, chemotherapy agents induce ROS and hence caused oxidative stress (Victorino et al. 2014). ROS accumulation in mitochondria may suppress the mitochondrial respiration chain and subsequently caused apoptotic cell death and mitochondrial membrane rupture (Tsuchiya et al. 2015; Gogvadze et al. 2009). A moderate elevation in ROS level was observed both in 5-FU alone and allicin groups. The ROS level has increased dramatically when the hepatocellular carcinoma cell lines are treated in combination. This finding implied the synergistic effect of ROS in combined treatment (Zou et al. 2016).

A previous study also had demonstrated that phytic acid exhibit a synergized effect along with tamoxifen and doxorubicin to suppress the proliferation of breast cancer (Tantivejkul et al. 2003). This finding indicates that phytic acid may counteract drug resistance usually observed in tumor cells and thus suggesting that it might be a useful adjunct. Interestingly, another study conducted in withanolides from *Withania somnifera* in vitro exhibited a significant reduction of human colon, breast, and lung cancer cell lines compared to that of standard drug, doxorubicin. Withaferin A, derived from the roots of *Withania somnifera*, exhibited to be more effective than doxorubicin (Jayaprakasam et al. 2003).

5.8 Conclusions and Future Prospects

Anticancer agents discovered from plant-derived compounds play a vitally important role in the treatment of cancer. Plant-derived compounds exert good immunomodulatory and antioxidant properties leading to anticancer activity. Plant-derived compounds may not serve as drugs, however they hold a great promise and indirectly provide leads in future use as a potential anticancer agents. Plant-derived compounds such as vinca alkaloids and its semisynthetic analogues and curcumin, colchicine, EGCG, betulinic acid, and podophyllotoxin derivatives have significantly affected cancer research in many aspects. They assist the researchers to gain a better understanding of the disease, providing new and efficient therapy in the development of future anticancer drugs and new mechanisms of action. Plants

represent an enormous diversity on earth; however, only a minute fraction of those have been identified. Therefore, it is expected that plants may provide potential bioactive components against numerous diseases, particularly cancer. The potential implication of the plant-derived compounds which replace conventional therapies could be significant and is warranted to be elucidated in long-term clinical trials.

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