Chapter 4
Elucidation of Mechanisms of Anticancer Plant Compounds Against the Tumor Cells

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Abstract Cancer is one of the noncommunicable diseases which is the second leading cause of deaths throughout the world. Chemotherapy is the major treatment approach, however, with a limited success rate accompanied by secondary adverse health effects. Moreover, in recent years, about 30–80% of cancer patients are developing resistance to chemotherapeutic drugs. Therefore, phytoconstituents have attained much attention among the researchers because of their effective multiple targeted cytotoxicity with a tolerable side effects and chemosensitizing potential. These are known to exhibit their anticancer activities in various ways of molecular mechanisms of action, such as arresting of cell cycle, inhibiting angiogenesis, inhibiting enzymes (cyclooxygenase, caspases, kinase matrix metalloproteinase (MMP), poly(ADP-ribose) polymerase 1 (PARP-1), etc.), inhibiting transcription factors, suppressing pro-inflammatory signaling pathways, inhibiting lipid signals, and inhibiting heat shock proteins. Though scientific evidences have suggested many plant compounds with chemopreventive potential, understanding the issues related to exposure time, bioavailability, toxic effects, and mechanisms of action will certainly help to identify the leads and utilize them against various cancer types. The present chapter deals with the anticancer effect of several compounds of plant origin and their mechanisms of action.

Keywords Anticancer plants · Apoptosis · Cell cycle · Inflammation · Transcription factors

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4.1 Introduction

Cancer is the second major noncommunicable disease and it caused about 8.2 million deaths in 2012 (Torre et al. 2015). Cancer is defined as a group of diseases in which normal tissue or organ is invaded by abnormal dividing cells. If left untreated, it spreads throughout the human body and even results in loss of human life (Eid et al. 2015). Carcinogenesis is the metabolic process, in which normal cells are transformed into cancer cells through three major stages such as initiation, promotion, and progression. The initiation (first) stage occurs in the normal cells due to exposure to carcinogenic (procarcinogens, epigenetic carcinogens, genotoxic carcinogens, etc.) or mutagenic (physical and chemical) agents. However, this first stage alone is not enough for tumor formation. In promotion (second) stage, tumor promoter agents help to convert the initiated cells into tumor cells. This second stage occurs very slowly, and it even takes several months to years depending upon changes in diet and lifestyle of the individual person. Progression (third/final) stage converts the tumor cells into high-degree malignant cells. At this progression stage, human diet has less impact on tumor progression (Reddy et al. 2003; Rajesh et al. 2015). The cancer incidence cases have been reported more from the developed countries compared to that of developing countries. Similarly, in the developing countries, breast, lung, and colorectal cancers are reported more among females (Jemal et al. 2011). Various risk factors have been reported in the cancer development which includes age, geographic area, and race (Millimouno et al. 2014). Chemotherapy is the major treatment approach; however, in recent years 30–80% of cancer patients are developing resistance to chemotherapeutic drugs. Therefore, plant-based substances (phytoconstituents) have attained much attention among the researchers. The present chapter deals with the anticancer effect of several compounds of plant origin and their mechanisms of action.

4.2 Mechanisms Involved in Cancer Chemoprevention and Treatment

Plant-based substances have been reported to induce cell cycle arrest and apoptosis by targeting multiple cellular signaling pathways such as (1) p53 pathway, (2) nuclear factor-kappaB transcription factor pathway, (3) nuclear factor-related factor 2 signaling pathway, (4) growth factors pathway, (5) signal transducers and activators of transcription (STAT) pathway, (6) Wnt/β-catenin pathway, (7) hedgehog (SHH) signaling pathway, (8) phosphatidylinositol 3 kinases (PI3K) pathway, (9) cyclooxygenase 2/prostaglandin E2 (COX 2/PGE2) pathway, (10) mitogen-activated protein kinase (MAPK) signaling pathway, (11) Cripto 1 protein signaling pathway, and (12) hypoxia signaling pathway. Thus, by targeting/modulating the abovementioned cellular signaling pathways, anticancer activity has been successful achieved by plant-based substances (Millimouno et al. 2014).

4.2.1 Cell Cycle Arrest

The cell cycle is the metabolic process by which cell progress and division consist of several biochemical and molecular signaling pathways. It exhibits four important stages or phases.

1. G1 (Gap 1) phase in which the cell grows and prepares to synthesize deoxyribonucleic acid (DNA)
2. S (synthesis) phase in which the cell synthesizes DNA (genetic material)
3. G2 (Gap 2) phase in which the cell prepares to divide
4. M (mitosis) phase in which cell division occurs and finally phase is termed as G0 (resting phase) in which cell leaves the cell cycle and quit dividing them

Cyclin-dependent kinases (CDKs) are group of enzymes which regulate the cell cycle transitions. These enzymes contain two subunits, namely, catalytic subunit (CDK) and regulatory subunit (cyclin). Each phase of the cell cycle has individual CDK cyclin enzymatic activity as shown below:

1. CDK2 cyclin E and A regulates G1 to S phase transition.
2. CDK1 cyclin A regulates late S to G2 phase transition.
3. CDK1 cyclin B regulates G2 to M phase transition.

In mammalian cells, about 10 CDKs and 20 cyclins have been reported; interestingly not all participate in cell cycle regulation. In normal cells cell cycle machinery controls the cell proliferation, which also includes repair mechanism with them. In the case of cancer cells, cell cycle machinery loses control and results in uncontrolled cell proliferation (Collins et al. 1997; Hwang and Clurman 2005).

4.2.2 Apoptosis

Apoptosis is the process of active cell death resulting in the breakdown of cellular structures, without causing any immune or inflammatory response to the host. It is also referred as "programmed cell death," which occurs in the several physiological and pathological conditions (Cummings et al. 1997; Iannolo et al. 2008). It is characterized by biochemical and morphological hallmarks such as cell shrinkage, chromatin condensation, cytoplasmic membrane blebbing, and nuclear DNA fragmentation (Fulda and Debatin 2006). It is essential for embryonic development, tissue homeostasis, immune function, and tumor suppression especially in multicellular organisms (Iannolo et al. 2008). It usually maintains balances between pro-apoptotic (BAD or BAK, BAK and BID) and anti-apoptotic (Bcl-2 and Bcl-Xl) signals. The accumulation of pro-apoptotic signals leads to apoptosis induction. Defects in apoptotic pathways have been observed in several diseases, including tumor and neurodegenerative disorders (Lowe and Lin 2000). Three important biochemical events occur during apoptosis; they are (1) activation of caspases activity,

(2) breakdown of DNA and protein, and (3) membrane modifications due to phagocytes (Wong 2011). The process of apoptosis is mainly divided into two pathways: (1) intrinsic pathway mediated by molecules released from mitochondrial membrane and (2) extrinsic pathway triggered by death receptor.

4.2.2.1 Intrinsic Pathway of Apoptosis

The intrinsic pathway is activated by physical or chemical stimuli such as cell detachments, cytokines, DNA damage, growth factor deprivation, hypoxia, and/or other stress signals. These stimuli modulate mitochondrial functions such as increases the mitochondrial membrane potential (MMP) and releases the cytochrome C into the cytoplasm. This cytosolic cytochrome C in turn interacts/binds with apoptotic protease-activating factor 1 (Apaf 1) and pro-caspase 9 (zymogen). Pro-caspase 9 activates caspase cascade such as caspases 3, 6, and 7, leading to DNA fragmentation and cell death. B-cell leukemia/lymphoma 2 (Bcl2) family proteins play an important role in regulating the intrinsic pathway by inducing or preventing the release of cytochrome C (Lowe and Lin 2000; Iannolo et al. 2008; Millimouno et al. 2014).

4.2.2.2 Extrinsic Pathway of Apoptosis

The extrinsic pathway is activated, when a death ligand binds to the extracellular domains of the death receptor and leads directly to caspase activation. For instance, Fas ligand (FasL) binds with its respective receptor Fas receptor (also called as Apo 1 or CD95), which forms death-inducing signaling complex (DISC) which contains the specific adaptor protein, namely, Fas-associated death domain protein (FADD) and caspase 8. Caspase 8 in turn activates caspase 3 and apoptosis in type 1 cells. The extrinsic pathway is quite similar to the intrinsic apoptotic pathway, which is also caspase-dependent; the one and only difference is that apoptotic signaling is initiated through membrane-bound death receptors (Wajant 2002; Iannolo et al. 2008).

4.2.2.3 Caspase-Independent or ROS-Mediated Apoptosis Pathway

Reactive oxygen species (ROS) are generated due to physiologic stress which is associated with the production of oxidative species through intracellular damage to DNA, lipids, proteins, and RNA. During cellular redox the excessive generation of ROS in turn induces oxidative stress, loss of cell function, and apoptosis. Granzyme A (enzyme belonging to serine proteases family) directly induces the ROS generation which in turn results in caspase-independent mitochondrial damage. Then ROS drives the endoplasmic reticulum (ER)-associated SET complex into the nucleus, where it activates apoptosis. ROS also mediates poly(ADP-ribose) polymerase 1

(PARP-1) activation, which is needed for apoptosis-inducing factor (AIF) release from mitochondria. Thus, AIF is the main pro-apoptosis factor involved in caspase-independent apoptosis pathway (Martinvalet et al. 2005; Lieberman 2010).

4.2.3 Necrosis

Necrosis is the process of passive cell death resulting in the breakdown of cellular structures, caused by specific physiological and pathological stimuli such as tumor necrosis factor (TNF), TNF-related apoptosis-inducing ligand (TRAIL), lipopolysaccharides (LPS), oxidative stress, and DNA damage (via PARP). Necrosis is characterized by biochemical and morphological hallmarks such as loss of membrane integrity, cell swelling, permanent loss of mitochondrial membrane potential, and DNA fragmentation (post-lytic/late stage). Specific physiological and pathological stimuli activate receptor-interacting protein (RIP1) kinase. This RIP1 kinase directly/indirectly transduces signal to mitochondria which leads to mitochondrial permeability and transition. This mitochondrial damage enhances enzymes such as protease (calpains, cathepsin) and phospholipase activities and finally results in plasma membrane destruction (sign of necrotic cell death). In contrast to apoptosis process, the mode of cell death is required for tumor regression, and thus necrosis plays important in anticancer therapy (Proskuryakov and Gabai 2010).

4.2.4 p53 Pathway

p53 (tumor suppressor gene) is stimulated by cellular stress like carcinogens, hypoxia, ionizing radiation, oxidative stress, and UV radiation. It regulates the apoptosis, genomic integrity, cell cycle, and DNA repair caused due to genotoxic stresses. p53 binds to regulatory DNA sequences as a tetramer and transactivates genes involved in apoptosis in response to DNA damage (ASPP1/2, BAX, Fas, NOXA, p53AIP1, PERP, PIDD, PUMA), cell cycle arrest (p21, cyclin G1, GADD45, 14-3-3, reprimo), angiogenesis (BA11, GD-AIF, maspin, TSP1), and genetic stability (DDB2, MSH2, p21, XPC). About 40 different isoforms of the p53 family members have been reported so far. Among these, p73 plays a significant role during neurogenesis, whereas p63 is essential in skin, limb, and craniofacial development. Interestingly, some p53 isoforms have oncogenic potential, while others have tumor suppressor activity (Millimouno et al. 2014; Pflaum et al. 2014).

4.2.5 NF-κB Pathway

Nuclear factor-kappaB (NF-κB transcription factor) is stimulated by cellular stress like carcinogens, cytokines, endotoxins, ionizing radiation, oxidative stress (free radicals), and UV radiation. It is involved in tumor initiation and progression. NF-κB is usually present in the cytoplasm via association with its IκB (endogenous inhibitor of NF-κB), which further phosphorylated by IκB kinase (IKK). IKKa activates metastasis in prostate cancer by inhibiting maspin (mammary serine protease inhibitor) and stimulates angiogenesis via activating interleukin 8 (IL8) and vascular endothelial growth factor (VEGF). The accumulation of the IκBα leads to activation of anti-apoptotic NF-κB, resulting in apoptosis. NF-κB pathway plays significant role in carcinogenesis by transactivating genes involved in angiogenesis, apoptosis, cell proliferation, metastasis, and tumor cell invasion (Millimouno et al. 2014).

4.2.6 Nuclear Factor-Related Factor 2 (Nrf2) Signaling Pathway

Nrf2 (belongs to the Cap 'N' Collar family) plays an important role in transcriptional activation of phase II detoxification enzymes (glutathione S-transferases) and plays as an important regulator of cell survival both in normal and cancer cells. It protects against chemical carcinogen by decreasing the ROS content and DNA damage in cells. Its defense role has been reported against various diseases such as acute pulmonary injury, aging, cancer, cardiovascular disease, diabetes, inflammation, photooxidative stress, and pulmonary fibrosis. Similarly, relationships between p21, p62, and Nrf2 have been reported. Nrf2 activators (from phytochemicals) have been shown to induce the Nrf2-mediated defense mechanism by enhancing phase II detoxification enzymes, antioxidants, and (ABC) transporters; this in turn protects the carcinogenic stimuli (Jaramillo and Zhang 2013; Millimouno et al. 2014).

4.2.7 Growth Factor Pathway

Growth factors (GFs) and growth factor receptors (GFR) play a vital role in physiological conditions such as growth and differentiation, wound healing, etc. Growth factors like colony-stimulating factor (CSF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), and transforming growth factor (TGF) are few growth factors involved in carcinogenesis. Growth factor receptor activation leads to downstream signaling of PI3K-Akt and Ras-MAPK pathways and thus acts as target for numerous anticancer/antitumor agents. For instance, suramin (polysulfonated drug) inhibits the binding of growth factors like epidermal growth factor (EGF), fibroblast growth factor (FGF),

insulin-like growth factor (IGF1 and IGF2), nerve growth factor (NGF), platelet-derived growth factor (PDGF), and transforming growth factor (TGF-α) to their receptors and induces disassociation of bound growth factors from their respective receptors and thereby has exhibited anticancer activity against adrenal, prostate, and renal cancer (Rajkumar 2001; Millimouno et al. 2014).

4.2.8 Signal Transducers and Activators of Transcription (STAT) Pathway

STAT belongs to family members of interferon (IFN) signaling complex and plays a dual role as signal transduction and transcription activators. STATs are cytoplasmic proteins that are activated by tyrosine kinases resulting in phosphorylation and dimer formation and translocate into the nucleus to regulate the transcription of genes. Seven STAT family members have been reported so far; they are STATs 1, 2, 3, 4, 5a, 5b, and 6. STAT3 activation has been reported by both Janus kinase (JAK) and also by non-receptor tyrosine kinases (c-Src kinases). Thus, inhibition of JAK/STAT pathway has been recognized as novel chemopreventive and chemotherapeutic target (Millimouno et al. 2014; Xiong et al. 2014).

4.2.9 Wnt/β-Catenin Pathway

Wnt binds with frizzled family receptor (FZD) and leads to the cytoplasmic accumulation of β-catenin. Then β-catenin translocates into the nucleus, where it interacts with T-cell factor/lymphoid enhancer factor 1 (TCF/Lef 1) transcription complex and regulates the transcription of genes. Wnt/β-catenin pathway has been reported in several cancers, and Wnt inhibition has been recognized as new target for colorectal cancer treatment (Pai et al. 2017).

4.2.10 Hedgehog (SHH) Signaling Pathway

SHH (glycoprotein) binds and inactivates the patched 1 (PTCH1) receptor, which inhibits the protein smoothened (SMO) activity. This in turn leads to activation of glioma-associated (GLI) transcription factors. Then GLI translocates into the nucleus and regulates the transcription of genes. Abnormal hedgehog (SHH) signaling that has been reported in several cancers includes colorectal, glioma, pancreatic, and prostate carcinoma. GLI 1 small interfering RNA (siRNA) has been used to induce apoptosis in prostate cancer, and thus hedgehog (SHH) signaling has been recognized as new target for cancer treatment (Wang et al. 2012; Rimkus et al. 2016).

4.2.11 Phosphatidylinositol 3 Kinases (PI3K) Pathway

Activation of phosphatidylinositol 3 kinases (PI3K) leads to the production of phosphatidylinositols [P2 and P3 (Ptdlns 3, 4) and P3 (Ptdlns 5)], which are bound by Akt. Phosphatidylinositols are further activated by phosphoinositide-dependent protein kinase 1 (PDK1) and Akt. These activated phosphatidylinositols are translocated into the plasma membrane and regulate the cellular process. Phosphatidylinositol 3 kinases (PI3K) play a significant role in cellular transformation and cancer development, and thus inhibition of PI3K serves a new target for cancer therapy (Liu et al. 2009; Wang et al. 2012).

4.2.12 Cyclooxygenase 2/Prostaglandin E2 (COX 2/PGE2) Pathway

Inflammatory stimuli activate COX 2 activity, which in turn activates PGE2. This extracellular PGE2 binds with prostaglandin E2 (EP) receptors and initiates multiple intracellular signaling pathways. COX 2 is one of the pro-inflammatory mediators, found to be elevated at the early stage of tumorigenesis (Reader et al. 2011; Wang et al. 2012).

4.2.13 Mitogen-Activated Protein Kinase (MAPK) Signaling Pathway

The RAS (small G protein)/RAF (rapidly accelerated fibrosarcoma)/MEK (mitogen-activated protein kinase)/ERK (extracellular signal-regulated kinase) signaling pathway involves complex network that regulates the proliferation, differentiation, cell survival, and apoptosis. The ligand (e.g., cytokine, growth factor, or hormone) binds with receptor tyrosine kinase (RTK). In this pathway, three protein kinases play a major role, namely, mitogen-activated protein kinase kinase kinase (MAPKKK or BRAF) that phosphorylates and activates mitogen-activated protein kinase kinase (MAPKK or MEK), which in turn activates mitogen-activated protein kinase (MAPK or ERK). This activated ERK translocates into the nucleus and regulates the gene expression. Numerous inhibitors of components of this pathway have been reported and recognized as good therapeutic approach for melanoma treatment (Kolch 2000; McCain 2013). Similarly, genistein (soy-derived isoflavone) has been reported to inhibit cervical cancer (HeLa and CaSki) cells via by inhibiting ERK1/2 activity and activating p38 MAPK pathway (Kim et al. 2009).

4.2.14 Cripto 1 and Its Allied Protein Signaling Pathway

Cripto 1 (CR1) mediates several cellular processes such as angiogenesis, cell growth, fetal development, inflammation, invasion, migration, tumor formation, and wound repair. CR 1 is a mitogenic protein, also known as teratocarcinoma-derived growth factor 1 (TDGF 1). CR 1 binds with growth factor receptors such as 78 kD glucose-regulated protein (GRP 78) or heat shock 70 kD protein 5 (HSPA5) and mediates several signal transduction pathway that includes nodal-dependent (Smad2/3) and nodal-independent (Src/p44/42/Akt) pathways. CR 1 functions as a chaperone protein by inducing cellular signaling via Wnt/β catenin and Notch/Cbf 1 signal transduction pathways. In cancer cells, activin is inhibited by the complex formed between CR1, activin, and activin receptor type II (ActRII). Alantolactone (*Inula helenium*) has been reported to exhibit antitumor activity via by inhibiting the activin signaling pathway (Wang et al. 2012; Klauzinska et al. 2015).

4.2.15 Hypoxia Signaling Pathway

Hypoxia plays a significant role in the number of pathological conditions including aging, cancer, diabetes, and ischemia/stroke. Hypoxia-inducible factor (HIF) is the main transcriptional factor in nutrient stress signaling and otherwise known as oxygen-sensitive transcription factor. HIF also plays a major role in autophagy, cell invasion, intracellular pH regulation, and metabolism. HIF also regulates the expression of two key angiogenic factors, namely, VEGF-A and angiopoietin 2 (Ang 2). HIF activity is predominately regulated through posttranslational modifications and stabilization of HIF 1α and 2α proteins. HIF-α protein activity is regulated by two key oxygen sensing/depending enzymes, namely, hypoxia-inducible factor prolyl hydroxylase 2 (HIF-PH2 or PHD) and factor inhibiting HIF (FIH or asparaginyl hydroxylase). Stabilization of HIF 1α activates transcription of genes that involved in angiogenesis, dedifferentiation, and invasion which are all important factors/pathways in carcinogenesis. Thus HIF pathway components serve as potential therapeutic targets against cancers (Pouysségur et al. 2006; Brocato et al. 2014; Elks et al. 2015). Apart from the important mechanism listed above, there are few other mechanisms not discussed. For example, plants/plant-based substances are known to have multitarget activity against multidrug resistance (MDR)-related proteins, thus providing solution to overcome drug resistance problem (Eid et al. 2015).

4.3 Plants Having Anticancer Activity

Whole/crude extracts from plants (more than 120,000 plant extracts belongs to 6000 genera) have been widely studied in the past few decades, and several plants found to have anticancer/antitumor activity. Some of these plants have been clinically proven as anticancer agents, while few others have been used as tools to elucidate the biochemical/molecular mechanisms involved in the growth and regulation of cancers/tumors. Plants are known to exhibit a wide range/spectrum of mechanisms of action such as blockers of cell cycle progression, antagonists of mitogenic signaling, anti-metastasis, upregulators of the immune system, and inhibitors of blood vessel formation (Mans et al. 2000). Among different plant families reported, the 11 predominant plant families such as Fabaceae, Asteraceae, Zingiberaceae, Euphorbiaceae, Apocynaceae, Meliaceae, Solanaceae, Rutaceae, Moraceae, Liliaceae, and Myrtaceae have been shown to exhibit anticancer activity (Table 4.1).

4.4 Phytoconstituents Having Anticancer Activity

Phytoconstituents are potent in the treating several cancers/tumors. Alkaloids, flavonoids, polyphenols, and terpenes are the few chemical classes that have been reported for anticancer/antitumor activity. According to Batra and Sharma (2013), flavonoids have modulated several cellular events in cancer cells such as apoptosis, cell differentiation, cell proliferation and vascularization, etc. Vinblastine, honokiol, magnolol, wedelolactone, oridonin, alantolactone, and costunolide are the few classical examples for phytoconstituents having anticancer activity (Millimouno et al. 2014). Apart from phytoconstituents, some marine-based substances also known to have anticancer activity include aragusterol A, ascididemin, bryostatin1, discodermolide, fascaplysin, indanone, jaspamide, lyngbyabellin A, melophlins A and B, salinosporamide A, and spisulosine (Mayer and Gustafson 2003). In the present chapter, Table 4.2 summarizes those 165 phytoconstituents shown to have anticancer activity by modulating several cellular signaling pathways.

4.5 Conclusions and Future Prospects

Despite much therapeutic advancements in the understanding of carcinogenesis processes, cancer still remains as a major health issue around the global. Plants have been recognized as rich source of anticancer drugs. At present more than 60% of commercially available anticancer agents are directly or indirectly obtained from

Table 4.1 List of medicinal plants with anticancer potential

Botanical name	Family name	References
Abrus precatorius	Fabaceae	Rahman and Khan (2013)
Achyranthes aspera	Amaranthaceae	Prakash et al. (2013)
Acorus calamus	Acoraceae	Pandey and Madhuri (2009)
Actinidia chinensis	Actinidiaceae	Chavan et al. (2013)
Aegles marmelos	Rutaceae	Costa-Lotufo et al. (2005)
Aegiceras corniculatum	Myrsinaceae	Rahman and Khan (2013)
Agapanthus africanus	Agapanthaceae	Kaur et al. (2011)
Agave americana	Agavaceae	Prakash et al. (2013)
Aglaia silvestris	Meliaceae	Prakash et al. (2013)
Agrimonia pilosa	Rosaceae	Prakash et al. (2013)
Agropyron repens	Poaceae	Prakash et al. (2013)
Ailanthus altissima	Simaroubaceae	Prakash et al. (2013)
Akebia quinata	Lardizabalaceae	Prakash et al. (2013)
Alangium salviifolium	Alangiaceae	Rahman and Khan (2013)
Albizia lebbeck	Fabaceae	Jaikumar and Jasmine (2016)
Albizia amara	Fabaceae	Jaikumar and Jasmine (2016)
Allium bakeri	Alliaceae	Pandey and Madhuri (2009)
Allium cepa	Alliaceae	Chavan et al. (2013)
Allium sativum	Alliaceae	Prakash et al. (2013)
Aloe spp.	Asphodelaceae	Chavan et al. (2013)
Alphitonia zizyphoides	Rhamnaceae	Pandey and Madhuri (2009)
Alpinia galanga	Zingiberaceae	Prakash et al. (2013)
Alstonia scholaris	Apocynaceae	Pandey and Madhuri (2009)
Amoora rohituka	Meliaceae	Rahman and Khan (2013)
Amorphophallus campanulatus	Araceae	Pandey and Madhuri (2009)
Andrographis paniculata	Acanthaceae	Prakash et al. (2013)
Ananas comosus	Bromeliaceae	Chavan et al. (2013)
Angelica sinensis	Apiaceae	Chavan et al. (2013)
Annona muricata	Annonaceae	Prakash et al. (2013)
Annona squamosa	Annonaceae	Jaikumar and Jasmine (2016)
Aphanamixis polystachya	Meliaceae	Chavan et al. (2013)
Apium graveolens	Apiaceae	Kaur et al. (2011)
Arctium lappa	Asteraceae	Chavan et al. (2013)
Aristolochia contorta	Aristolochiaceae	Prakash et al. (2013)
Artemisia diffusa	Asteraceae	Ko and Moon (2015)
Artemisia monosperma	Asteraceae	Solowey et al. (2014)
Artocarpus heterophyllus	Moraceae	Jaikumar and Jasmine (2016)
Aspalathus linearis	Fabaceae	Reddy et al. (2003)
Aster tataricus	Asteraceae	Prakash et al. (2013)
Astragalus membranaceus	Fabaceae	Prakash et al. (2013)
Avicennia alba	Avicenniaceae	Pandey and Madhuri (2009)
Azadirachta indica	Meliaceae	Kamkaen et al. (2006)

(continued)

Table 4.1 (continued)

Botanical name	Family name	References
Bauhinia variegata	Fabaceae	Chavan et al. (2013)
Berberis aristata	Berberidaceae	Pandey and Madhuri (2009)
Betula utilis	Betulaceae	Chavan et al. (2013)
Bidens pilosa	Asteraceae	Prakash et al. (2013)
Bleckeria vitensis	Apocynaceae	Mans et al. (2000)
Blumea lacera	Asteraceae	Rahman and Khan (2013)
Boesenbergia pandurata	Zingiberaceae	Kamkaen et al. (2006)
Boesenbergia rotunda	Zingiberaceae	Rahman (2016)
Bolbostemma paniculatum	Cucurbitaceae	Prakash et al. (2013)
Broussonetia papyrifera	Moraceae	Jaikumar and Jasmine (2016)
Brucea antidysenterica	Simaraubaceae	Kaur et al. (2011)
Bruguiera exaristata	Rhizophoraceae	Pandey and Madhuri (2009)
Bruguiera gymnorrhiza	Rhizophoraceae	Rahman and Khan (2013)
Bruguiera parviflora	Rhizophoraceae	Pandey and Madhuri (2009)
Bryonia dioica	Cucurbitaceae	Prakash et al. (2013)
Bursera microphylla	Burseraceae	Kaur et al. (2011)
Caesalpinia bonduc	Caesalpiniaceae	Pandey and Madhuri (2009)
Cajanus cajan	Fabaceae	Pandey and Madhuri (2009)
Calophyllum inophyllum	Clusiaceae	Pandey and Madhuri (2009)
Calotropis procera	Asclepiadaceae	Rahman and Khan (2013)
Camellia sinensis	Theaceae	Prakash et al. (2013)
Camptotheca acuminata	Nyssaceae	Mans et al. (2000)
Canavalia ensiformis	Fabaceae	Prakash et al. (2013)
Cannabis sativa	Cannabinaceae	Prakash et al. (2013)
Catharanthus pusillus	Apocynaceae	Jaikumar and Jasmine (2016)
Catharanthus roseus	Apocynaceae	Mans et al. (2000)
Carissa opaca	Apocynaceae	Jaikumar and Jasmine (2016)
Cassia absus	Caesalpiniaceae	Pandey and Madhuri (2009)
Cassia garrettiana	Caesalpiniaceae	Jaikumar and Jasmine (2016)
Cayratia carnosa	Vitaceae	Pandey and Madhuri (2009)
Cedrus deodara	Pinaceae	Pandey and Madhuri (2009)
Ceiba pentandra	Bombacaceae	Pandey and Madhuri (2009)
Celtis africana	Ulmaceae	Pandey and Madhuri (2009)
Centaurea spp.	Asteraceae	Prakash et al. (2013)
Centella asiatica	Apiaceae	Prakash et al. (2013)
Cephalotaxus fortunei	Cephalotaxaceae	Basmadjian et al. (2014)
Cephalotaxus harringtonia	Cephalotaxaceae	Prakash et al. (2013)
Chelidonium majus	Papaveraceae	Prakash et al. (2013)
Chloranthus henryi	Chloranthaceae	Ko and Moon (2015)
Chimaphila umbellata	Ericaceae	Prakash et al. (2013)
Cichorium intybus	Asteraceae	Jaikumar and Jasmine (2016)
Cissus quadrangularis	Vitaceae	Pandey and Madhuri (2009)

(continued)

Table 4.1 (continued)

Botanical name	Family name	References
Citrus limon	Rutaceae	Pandey and Madhuri (2009)
Clausena excavata	Rutaceae	Rahman (2016)
Cleistanthus collinus	Euphorbiaceae	Kaur et al. (2011)
Colchicum luteum	Liliaceae	Chavan et al. (2013)
Combretum caffrum	Combretaceae	Prakash et al. (2013)
Coscinium fenestratum	Menispermaceae	Kamkaen et al. (2006)
Coix lacryma-jobi	Poaceae	Prakash et al. (2013)
Crocus sativus	Iridaceae	Samarghandian et al. (2011)
Croton lechleri	Euphorbiaceae	Kaur et al. (2011)
Curcuma domestica	Zingiberaceae	Prakash et al. (2013)
Curcuma longa	Zingiberaceae	Gali-Muhtasib et al. (2015)
Curcuma wenyujin	Zingiberaceae	Ko and Moon (2015)
Curcuma zedoaria	Zingiberaceae	Reddy et al. (2003)
Curtisia dentata	Cornaceae	Pandey and Madhuri (2009)
Cuscuta reflexa	Convolvulaceae	Rahman and Khan (2013)
Cycas rumphii	Cycadaceae	Pandey and Madhuri (2009)
Cyclopia intermedia	Fabaceae	Reddy et al. (2003)
Cynodon dactylon	Poaceae	Jaikumar and Jasmine (2016)
Daphne mezereum	Thymelaeaceae	Prakash et al. (2013)
Datura metel	Solanaceae	Jaikumar and Jasmine (2016)
Decaspermum fruticosum	Myrtaceae	Pandey and Madhuri (2009)
Dendrobium moniliforme	Orchidaceae	Ko and Moon (2015)
Dendrophthoe falcata	Loranthaceae	Rahman and Khan (2013)
Dioscorea bulbifera	Dioscoreaceae	Rahman and Khan (2013)
Diphylleia grayi	Berberidaceae	Kaur et al. (2011)
Dracunculus vulgaris	Araceae	Jaikumar and Jasmine (2016)
Dryopteris crassirhizoma	Polypodiaceae	Prakash et al. (2013)
Duranta serratifolia	Verbenaceae	Jaikumar and Jasmine (2016)
Dysoxylum binectariferum	Meliaceae	Mans et al. (2000)
Dysoxylum caulostachyum	Meliaceae	Jaikumar and Jasmine (2016)
Echinacea angustifolia	Asteraceae	Chavan et al. (2013)
Echinops setifer	Asteraceae	Prakash et al. (2013)
Elaeis guineensis	Arecaceae	Jaikumar and Jasmine (2016)
Elephantopus scaber	Asteraceae	Jaikumar and Jasmine (2016)
Embelia ribes	Myrsinaceae	Rahman and Khan (2013)
Erythronium americanum	Liliaceae	Prakash et al. (2013)
Erythroxylum pervillei	Erythroxylaceae	Prakash et al. (2013)
Eucalyptus grandis	Myrtaceae	Reddy et al. (2003)
Eucomis autumnalis	Hyacinthaceae	Pandey and Madhuri (2009)
Eugenia aquea	Myrtaceae	Jaikumar and Jasmine (2016)
Eugenia caryophyllata	Myrtaceae	Pandey and Madhuri (2009)
Euonymus alatus	Celastraceae	Prakash et al. (2013)

(continued)

Table 4.1 (continued)

Botanical name	Family name	References
Eupatorium cannabinum	Asteraceae	Prakash et al. (2013)
Euphorbia ingens	Euphorbiaceae	Pandey and Madhuri (2009)
Euphorbia peplus	Euphorbiaceae	Basmadjian et al. (2014)
Euphorbia semiperfoliata	Euphorbiaceae	Kaur et al. (2011)
Equisetum hyemale	Equisetaceae	Pandey and Madhuri (2009)
Fagopyrum esculentum	Polygonaceae	Chavan et al. (2013)
Fallopia japonica	Polygonaceae	Gali-Muhtasib et al. (2015)
Ficus benghalensis	Moraceae	Rahman and Khan (2013)
Ficus religiosa	Moraceae	Rahman and Khan (2013)
Fragaria vesca	Rosaceae	Prakash et al. (2013)
Fritillaria thunbergii	Liliaceae	Prakash et al. (2013)
Galium aparine	Rubiaceae	Prakash et al. (2013)
Garcinia celebica	Clusiaceace	Jaikumar and Jasmine (2016)
Gardenia jasminoides	Rubiaceae	Ko and Moon (2015)
Genista tinctoria	Fabaceae	Gali-Muhtasib et al. (2015)
Geranium robertianum	Geraniaceae	Pandey and Madhuri (2009)
Ginkgo biloba	Ginkgoaceae	Chavan et al. (2013)
Glycyrrhiza glabra	Fabaceae	Pandey and Madhuri (2009)
Glycine max	Fabaceae	Suthar et al. (2001)
Gossypium hirsutum	Malvaceae	Prakash et al. (2013)
Gunnera perpensa	Gunneraceae	Kaur et al. (2011)
Gymnosporia rothiana	Celastraceae	Reddy et al. (2003)
Gynura pseudochina	Asteraceae	Pandey and Madhuri (2009)
Harringtonia cephalotaxus	Cephalotaxaceae	Mans et al. (2000)
Hibiscus cannabinus	Malvaceae	Rahman (2016)
Hibiscus tiliaceus	Malvaceae	Rahman and Khan (2013)
Hydrastis canadensis	Ranunculaceae	Prakash et al. (2013)
Hypericum perforatum	Hypericaceae	Prakash et al. (2013)
Hypoxis colchicifolia	Hypoxidaceae	Kaur et al. (2011)
Hypoxis hemerocallidea	Hypoxidaceae	Pandey and Madhuri (2009)
Indigofera tinctoria	Fabaceae	Kaur et al. (2011)
Inula graveolens	Asteraceae	Jaikumar and Jasmine (2016)
Ipomoea batatas	Convolvulaceae	Mans et al. (2000)
Jatropha gossypiifolia	Euphorbiaceae	Rahman and Khan (2013)
Juncus effuses	Juncaceae	Prakash et al. (2013)
Justicia procumbens	Acanthaceae	Kaur et al. (2011)
Kaempferia parviflora	Zingiberaceae	Rahman and Khan (2013)
Lantana camara	Verbenaceae	Rahman and Khan (2013)
Larrea tridentate	Zygophyllaceae	Prakash et al. (2013)
Lavandula dentata	Lamiaceae	Jaikumar and Jasmine (2016)
Leea indica	Leeaceae	Rahman and Khan (2013)
Lepisorus contortus	Polypodiaceae	Yang et al. (2011)

(continued)

Table 4.1 (continued)

Botanical name	Family name	References
Limonia acidissima	Rutaceae	Jaikumar and Jasmine (2016)
Linum album	Linaceae	Kaur et al. (2011)
Linum usitatissimum	Linaceae	Chavan et al. (2013)
Lithospermum erythrorhizon	Boraginaceae	Demain and Vaishnav (2011)
Lonicera japonica	Caprifoliaceae	Prakash et al. (2013)
Luisia tenuifolia	Orchidaceae	Pandey and Madhuri (2009)
Maclura pomifera	Moraceae	Greenwell and Rahman (2015)
Macrosolen parasiticus	Loranthaceaea	Jaikumar and Jasmine (2016)
Mallotus philippensis	Euphorbiaceae	Pandey and Madhuri (2009)
Malus domestica	Rosaceae	Chavan et al. (2013)
Mangifera indica	Anacardiaceae	Prakash et al. (2013)
Manilkara zapota	Sapotaceae	Jaikumar and Jasmine (2016)
Marrubium vulgare	Lamiaceae	Jaikumar and Jasmine (2016)
Martynia annua	Martyniaceae	Pandey and Madhuri (2009)
Medicago sativa	Fabaceae	Prakash et al. (2013)
Melastoma malabathricum	Melastomataceae	Jaikumar and Jasmine (2016)
Mentha arvensis	Lamiaceae	Pandey and Madhuri (2009)
Mollugo pentaphylla	Molluginaceae	Rahman and Khan (2013)
Morinda citrifolia	Rubiaceae	Chavan et al. (2013)
Moringa oleifera	Moringaceae	Costa-Lotufo et al. (2005)
Moringa peregrina	Moringaceae	El-Alfy et al. (2011)
Murraya koenigii	Rutaceae	Rahman and Khan (2013)
Mussaenda raiateenisis	Rubiaceae	Pandey and Madhuri (2009)
Nelumbo nucifera	Nelumbonaceae	Rahman and Khan (2013)
Nervilia fordii	Orchidaceae	Prakash et al. (2013)
Nigella sativa	Ranunculaceae	Chavan et al. (2013)
Nyctanthes arbortristis	Oleaceae	Rahman and Khan (2013)
Ochrosia elliptica	Apocynaceae	Chavan et al. (2013)
Ocimum sanctum	Lamiaceae	Chavan et al. (2013)
Oldenlandia diffusa	Rubiaceae	Chavan et al. (2013)
Olea europaea	Oleaceae	Prakash et al. (2013)
Origanum dayi	Lamiaceae	Solowey et al. (2014)
Ornithogalum spp.	Asparagaceae	Reddy et al. (2003)
Oroxylum indicum	Bignoniaceae	Costa-Lotufo et al. (2005)
Oxalis corniculata	Oxalidaceae	Rahman and Khan (2013)
Panax ginseng	Araliaceae	Chavan et al. (2013)
Panax quinquefolium	Araliaceae	Prakash et al. (2013)
Pandanus odoratissimus	Pandanaceae	Pandey and Madhuri (2009)
Paris polyphylla	Melanthiaceae	Kaur et al. (2011)
Pastinaca sativa	Apiaceae	Pandey and Madhuri (2009)
Penstemon deustus	Scrophulariaceae	Kaur et al. (2011)
Periploca aphylla	Asciepiadaceae	Pandey and Madhuri (2009)

(continued)

Table 4.1 (continued)

Botanical name	Family name	References
Phaleria macrocarpa	Thymelaeaceae	Prakash et al. (2013)
Phellodendron amurense	Rutaceae	Ko and Moon (2015)
Phyllanthus emblica	Euphorbiaceae	Jaikumar and Jasmine (2016)
Physalis angulata	Solanaceae	Pandey and Madhuri (2009)
Physalis minima	Solanaceae	Rahman and Khan (2013)
Picrorhiza kurroa	Scrophulariaceae	Chavan et al. (2013)
Piper cubeba	Piperaceae	Jaikumar and Jasmine (2016)
Piper longum	Piperaceae	Pandey and Madhuri (2009)
Piper nigrum	Piperaceae	Jaikumar and Jasmine (2016)
Pittosporum viridiflorum	Pittosporaceae	Pandey and Madhuri (2009)
Plumbago zeylanica	Plumbaginaceae	Chavan et al. (2013)
Podophyllum emodi	Berberidaceae	Mans et al. (2000)
Podophyllum peltatum	Berberidaceae	Mans et al. (2000)
Polygala senega	Polygalaceae	Pandey and Madhuri (2009)
Polygonatum multiflorum	Liliaceae	Prakash et al. (2013)
Polygonum cuspidatum	Polygonaceae	Kaur et al. (2011)
Pongamia pinnata	Fabaceae	Pandey and Madhuri (2009)
Potentilla chinensis	Rolsaaceae	Prakash et al. (2013)
Premna obtusifolia	Verbenaceae	Pandey and Madhuri (2009)
Primula auriculata	Primulaceae	Jaikumar and Jasmine (2016)
Prosopis cineraria	Fabaceae	Jaikumar and Jasmine (2016)
Prunella vulgaris	Lamiaceae	Chavan et al. (2013)
Prunus spp.	Rosaceae	Pandey and Madhuri (2009)
Psoralea corylifolia	Fabaceae	Chavan et al. (2013)
Psychotria insularum	Rubiaceae	Pandey and Madhuri (2009)
Psychotria valentonic	Rubiaceae	Jaikumar and Jasmine (2016)
Pteris multifida	Pteridaceace	Jaikumar and Jasmine (2016)
Pterocarpus santalinus	Fabaceae	Rahman and Khan (2013)
Pterospermum acerifolium	Sterculiaceae	Pandey and Madhuri (2009)
Punica granatum	Punicaceae	Chavan et al. (2013)
Pygeum africanum	Boraginaceae	Prakash et al. (2013)
Pyrus malus	Rosaceae	Prakash et al. (2013)
Raphanus sativus	Brassicaceae	Prakash et al. (2013)
Rhaphidophora pertusa	Araceae	Pandey and Madhuri (2009)
Rhus chinensis	Anacardiaceae	Prakash et al. (2013)
Rubia cordifolia	Rubiaceae	Prakash et al. (2013)
Rubus idaeus	Rosaceae	Prakash et al. (2013)
Salix tetrasperma	Salicaceae	Rahman and Khan (2013)
Salvadora persica	Salvadoraceae	Jaikumar and Jasmine (2016)
Saururus chinensis	Saururaceae	Ko and Moon (2015)
Saussurea lappa	Asteraceae	Chavan et al. (2013)
Scilla natalensis	Hyacinthaceae	Prakash et al. (2013)

(continued)

Table 4.1 (continued)

Botanical name	Family name	References
Scrophularia variegata	Scrophulariaceae	Jaikumar and Jasmine (2016)
Scrophularia nodosa	Scrophulariaceae	Prakash et al. (2013)
Scutellaria spp.	Lamiaceae	Prakash et al. (2013)
Sesamum indicum	Pedaliaceae	Pandey and Madhuri (2009)
Sesbania grandiflora	Fabaceae	Jaikumar and Jasmine (2016)
Silybum marianum	Asteraceae	Prakash et al. (2013)
Smilax china	Smilacaceae	Prakash et al. (2013)
Smilax chinensis	Liliaceae	Prakash et al. (2013)
Solanum anguivi	Solanaceae	Jaikumar and Jasmine (2016)
Solanum nigrum	Solanaceae	Rahman and Khan (2013)
Solanum torvum	Solanaceae	Jaikumar and Jasmine (2016)
Sonchus oleraceus	Asteraceae	Pandey and Madhuri (2009)
Strychnos nuxvomica	Loganiaceae	Prakash et al. (2013)
Sutherlandia frutescens	Fabaceae	Pandey and Madhuri (2009)
Syzygium cumini	Myrtaceae	Jaikumar and Jasmine (2016)
Tabebuia spp.	Bignoniaceae	Prakash et al. (2013)
Taraxacum officinale	Asteraceae	Prakash et al. (2013)
Taxodium distichum	Cupressaceae	Pandey and Madhuri (2009)
Taxus brevifolia	Taxaceae	Mans et al. (2000)
Tecoma stans	Bignoniaceae	Jaikumar and Jasmine (2016)
Tephrosia purpurea	Fabaceae	Jaikumar and Jasmine (2016)
Terminalia chebula	Combretaceae	Prakash et al. (2013)
Tetragonia tetragonioides	Aizoaceae	Pandey and Madhuri (2009)
Tetrastigma serrulatum	Vitaceae	Pandey and Madhuri (2009)
Thespesia populnea	Malvaceae	Pandey and Madhuri (2009)
Thuja occidentalis	Cupressaceae	Prakash et al. (2013)
Thymus vulgaris	Lamiaceae	Prakash et al. (2013)
Tinospora cordifolia	Menispermaceae	Chavan et al. (2013)
Tinospora crispa	Menispermaceae	Rahman and Khan (2013)
Toona ciliata	Meliaceae	Jaikumar and Jasmine (2016)
Tragia involucrata	Euphorbiaceae	Rahman and Khan (2013)
Trapa natans	Trapaceae	Pandey and Madhuri (2009)
Trichosanthes kirilowii	Cucurbitaceae	Pandey and Madhuri (2009)
Trifolium pratense	Fabaceae	Prakash et al. (2013)
Trigonella foenum-gracecum	Fabaceae	Jaikumar and Jasmine (2016)
Typhonium flagelliforme	Araceae	Rahman (2016)
Urtica membranacea	Urticaceae	Solowey et al. (2014)
Uncaria tomentosa	Rubiaceae	Reddy et al. (2003)
Vernonia amygdalina	Asteraceae	Prakash et al. (2013)
Vernonia cinerea	Asteraceae	Pandey and Madhuri (2009)
Vetiveriazizanioides	Poaceae	Jaikumar and Jasmine (2016)
Viscum album	Santalaceae (Viscaceae)	Chavan et al. (2013)

(continued)

Table 4.1 (continued)

Botanical name	Family name	References
Vitex negundo	Verbenaceae	Rahman and Khan (2013)
Vitex rotundifolia	Verbenaceae	Prakash et al. (2013)
Vitex trifolia	Verbenaceae	Jaikumar and Jasmine (2016)
Wikstroemia viridi	Thymelaeaceae	Kaur et al. (2011)
Withania somnifera	Solanaceae	Prakash et al. (2013)
Wrightia tinctoria	Apocynaceae	Jaikumar and Jasmine (2016)
Zingiber cassumunar	Zingiberaceae	Rahman (2016)
Zingiber officinale	Zingiberaceae	Prakash et al. (2013)
Zingiber zerumbet	Zingiberaceae	Rahman (2016)
Zizyphus spp.	Rhamnaceae	Prakash et al. (2013)
Miscellaneous		
Chlorella pyrenoidosa	Oocystaceae	Chavan et al. (2013)
Coriolus versicolor	Polyporaceae	Reddy et al. (2003)
Ecteinascidia turbinata	Perophoridae	Basmadjian et al. (2014)
Gyrophora esculenta	Umbilicariaceae	Chavan et al. (2013)
Halichondria okadai	Halichondriidae	Basmadjian et al. (2014)
Lentinus edodes	Marasmiaceae	Chavan et al. (2013)
Mylabris phalerata	Meloidae	Chavan et al. (2013)
Undaria pinnatifida	Alariaceae	Reddy et al. (2003)

natural sources including plants. New technologies in isolating bioactive compounds and screening for anticancer activities (high throughput screening) have been developed and studied for natural products. Further, scientific evidences have revealed that anticancer phyto-drugs prevent and destroy cancerous cells through the involvement of various kinds of molecular mechanisms of action. Simultaneously, new challenges are emerging due to safety concern, increased cases of drug resistance, and cost of tumor diagnosis. Apart from these, rapid growing obesity rate and increasing addict to smoking has been recognized as two more challenges/risk factors leading to high cancer incidence. The gold standards for assessing the safety and efficacy of drugs must be followed strictly and uniformly across the globe. In this regard, more number of *in vivo* studies should be encouraged to access the potential of lead plant molecules in future. Similarly, the placebo-controlled clinical trials must be carried out universally to have statistical significance value. In conclusion, natural product research is fascinating approach for discovering novel bioactive compounds with unique chemical structure and unique mode of action against different cancer types.

Table 4.2 List of phytochemicals with anticancer potential

Compound name	Mechanism of actions	References
Abrin A and B	Cytotoxicity, growth inhibition	Rahman and Khan (2013)
Ailanthone	Apoptosis induction and cell cycle arrest	Zhuo et al. (2015)
Alantolactone	Apoptosis induction and cell cycle arrest	Millimouno et al. (2014)
Allicin	Cell cycle arrest (S to G2/M phase)	Reddy et al. (2003)
Aloesin	Apoptosis induction, cell cycle arrest, anti-invasion and anti-migration activity	Zhang et al. (2017)
Amarbelin	Cytotoxicity, p53 and Bax upregulation, Bcl-2 and survivin downregulation	Rahman and Khan (2013)
9-Aminocampothecin	Inhibition of topoisomerase I	Mans et al. (2000)
Amooranin	Cytotoxicity, cell cycle, arrest (G2/M phase), caspase-activated apoptosis, growth inhibition through cyclin-dependent kinases (CDK2 and CDK1)	Rahman and Khan (2013)
Amygdalin	Apoptosis induction	Song and Xu (2014)
β-Amyrin	Cytotoxicity	Rahman and Khan (2013)
Anacardic acid	Cytotoxicity	Kubo et al. (1993)
Anthocyanidin	Induction of apoptosis, inhibition H3 and H4 acetylation, and inhibition Rb protein phosphorylation	Rahman and Khan (2013)
Apigenin	Cytotoxicity	Rahman and Khan (2013)
Arbutin	Apoptosis induction	Nawarak et al. (2009)
Arctigenin	Antiproliferative effect	Hirano et al. (1994)
Asiaticoside	Apoptosis induction	Huang et al. (2004)
Asimilobine	Cytotoxicity, p21-dependent cell cycle arrest (G1 phase), inhibition of growth	Rahman and Khan (2013)
Astaxanthin	Antiproliferation, apoptosis induction, and anti-invasion activity	Zhang and Wang (2015)
Astragalin	Cytotoxicity, p21-dependent cell cycle arrest (G1 phase), inhibition of growth	Rahman and Khan (2013)
Baicalein	Antiproliferative effect	Hirano et al. (1994)
Berberine	Apoptosis induction, complexes with DNA	Reddy et al. (2003)
Bergenin	Cytotoxicity, p53 and Bax upregulation, Bcl-2 and survivin downregulation	Rahman and Khan (2013)

(continued)

Table 4.2 (continued)

Compound name	Mechanism of actions	References
Betulinic acid	Apoptosis induction by affecting the mitochondrial membrane permeability complex, enhancing the release of cytochrome C, regulating Bcl-2 family members, inhibiting NF-κB activity and anti-metastasis	Wang et al. (2012)
Biochanin A	Antiproliferation, apoptosis induction, anti-invasion and anti-migration activity	Bhardwaj et al. (2014)
Bruceantin	c-Myc (oncoprotein) downregulation	Cragg and Newman (2005)
Caffeic acid	Apoptosis induction via by the mitochondrial apoptotic pathway and caspase-3 activation	Chang et al. (2010)
27-*O-trans* caffeoylcylicodiscic acid	Cytotoxicity, growth inhibition	Rahman and Khan (2013)
Camaraside	Cell proliferation inhibition, caspase-3-dependent apoptosis, Bcl-2 downregulation and Bax upregulation	Rahman and Khan (2013)
Capsaicin	Apoptosis induction and cell cycle arrest	Ko and Moon (2015)
Cardols	Cytotoxicity	Kubo et al. (1993)
Carnosic acid	Forms DNA adducts	Reddy et al. (2003)
Catechin	Cytotoxicity	Rahman and Khan (2013)
Caryatin	Apoptosis induction	Rahman and Khan (2013)
β-Caryophyllene	Cytotoxicity	Rahman and Khan (2013)
Casticin	Antiproliferation effect	Millimouno et al. (2014)
Chalcinasterol	Cytotoxicity	Rahman and Khan (2013)
Chebulinic acid	Cytotoxicity	Rahman and Khan (2013)
Cholestane glycoside	Apoptosis induction	Reddy et al. (2003)
Chrysin	Antiproliferation, apoptosis induction, caspase activation and inactivation of Akt signaling pathway	Khoo et al. (2010)
Cleistanthin A	Inhibition of DNA synthesis and cell division	Pradheepkumar and Shanmugam (1999)
Colchicine	Hinders microtubule formation, inhibits cell cycle progression, and induces apoptosis	Wang et al. (2012)
Costunolide	Apoptosis induction and cell cycle arrest	Millimouno et al. (2014)

(continued)

Table 4.2 (continued)

Compound name	Mechanism of actions	References
Crocetin	Inhibition of growth, induction of apoptosis, and hindering growth factor signaling pathways	Wang et al. (2012)
β-Cryptoxanthin	Stimulates expression of RB and p73 gene (tumor suppressor gene)	Reddy et al. (2003)
Coumarin	Cytotoxicity, p53 and Bax upregulation, Bcl-2 and survivin downregulation	Rahman and Khan (2013)
Cubebin	Apoptosis induction	Rajalekshmi et al. (2016)
Curcumin	Apoptosis induction and regulation of multiple cell signaling pathways including cell proliferation pathway (cyclin D1, c-myc), cell survival pathway (Bcl-2, Bcl-x, cFLIP, XIAP, c-IAP1), caspase activation pathway (caspase-8, 3, 9), tumor suppressor pathway (p53, p21), death receptor pathway (DR4, DR5), mitochondrial pathways, and protein kinase pathway (JNK, *Akt*, and AMPK)	Wang et al. (2012)
Daidzein	Antiproliferative effect	Hirano et al. (1994)
Dayscyphin C	Cytotoxicity	Khanna and Kannabiran (2009)
Delphinidin	Antiproliferation (cell cycle arrest, apoptosis) effect	Bin Hafeez et al. (2008)
Denbinobin	Apoptosis induction	Ko and Moon (2015)
Diosbulbin B	Apoptosis induction	Rahman and Khan (2013)
Dulcitol	Cytotoxicity, p53 and Bax upregulation, Bcl-2 and survivin downregulation	Rahman and Khan (2013)
β-Elemene	Cell cycle arrest (S to G2/M phase)	Reddy et al. (2003)
Ellagic acid	Apoptosis induction and inhibition of NF-κB activity	Edderkaoui et al. (2008)
Elliptinium	Inhibition of topoisomerase II	Mans et al. (2000)
Embelin	Apoptosis induction, cell cycle arrest, downregulation of Bcl-2, Bcl-xL, survivin, IAP-1, IAP-2, cyclin D1, and caspase-3 activation	Rahman and Khan (2013)
Epigallocatechin-3-gallate	Apoptosis induction, cell cycle arrest	Reddy et al. (2003)
Epipodophyllotoxin	Pro-apoptotic effects, cell cycle interference	Greenwell and Rahman (2015)
Etoposide	Inhibition of topoisomerase II	Mans et al. (2000)
Euglobal-G1	Apoptosis induction	Reddy et al. (2003)

(continued)

Table 4.2 (continued)

Compound name	Mechanism of actions	References
Evodiamine	Antiproliferation (cell cycle arrest, apoptosis induction) effect	Millimouno et al. (2014)
Falodone	Antiproliferative effect, cytotoxicity	Rahman and Khan (2013)
Fangchinoline	Antiproliferation (cell cycle arrest, apoptosis induction) effect	Ko and Moon (2015)
E-*β*-farnesene	Cytotoxicity	Rahman and Khan (2013)
Ferulic acid	Modulates mitogenic signaling and induction of cell cycle (G1) arrest and apoptosis	Reddy et al. (2003)
Fisetin	Cell cycle arrest (G1 phase) and disrupted Wnt/*β*-catenin signaling	Wang et al. (2012)
Flavopiridol	Inhibition of cyclin-dependent kinases	Mans et al. (2000)
Formononetin	Apoptosis induction and inhibition of *Akt* signaling pathway	Jin et al. (2014)
Friedelin	Cytotoxicity	Rahman and Khan (2013)
Furanodiene	Cell cycle transition, anti-invasion, anti-metastasis	Ko and Moon (2015)
Gallic acid	Cytotoxicity	Rahman and Khan (2013)
Galangin	Apoptosis induction and anti-invasion	Cao et al. (2016)
Genipin	Apoptosis induction, inhibiting invasion/metastasis	Ko and Moon (2015)
Gentisic acid	Induction of apoptosis, inhibition H3 and H4 acetylation, and inhibition Rb protein phosphorylation	Rahman and Khan (2013)
Genistein	Regulation of multiple signaling pathways (PTK, *Akt*, NF-κB, MMP, and Bax/Bcl-2)	Lee et al. (2012)
Glycyrrhizic acid	Antiproliferation, apoptosis induction, and Fas and FasL upregulation	Haghshenas et al. (2014)
Gingerol	Apoptosis induction	Wang et al. (2012)
Ginsenoside	Apoptosis, cell cycle transition	Ko and Moon (2015)
Gymnemagenol	Cytotoxicity	Khanna and Kannabiran (2009)
Halofuginone	Antiproliferative effect	Juárez(2014)
Homoharringtonine	Inhibition of DNA polymerase α	Mans et al. (2000)
Honokiol	Apoptosis induction	Juárez (2014)
α-Humulene	Cytotoxicity	Rahman and Khan (2013)

(continued)

Table 4.2 (continued)

Compound name	Mechanism of actions	References
Hypericin	Photocytotoxicity, induction of apoptosis and necrosis	Agostinis et al. 2002.
Indirubin	Inhibition of cyclin-dependent kinases (CDKs)	Cragg and Newman (2005)
4-Ipomeanol	Cytochrome P-450-mediated conversion into DNA-binding metabolites	Mans et al. (2000)
Isoalantolactone	Antiproliferative effect	Millimouno et al. (2014)
Isoliensinine	Cytotoxicity, p21-dependent cell cycle arrest (G1 phase), and inhibition of growth	Rahman and Khan (2013)
Isoliquiritigenin	Antiproliferation (cell cycle arrest, apoptosis induction) effect, anti-invasion and anti-metastasis activity	Peng et al. (2015)
Jaceosidin	Antiproliferation (cell cycle arrest, apoptosis induction) effect	Millimouno et al. (2014)
Jatrophone	Antiproliferative effect and cytotoxicity	Rahman and Khan (2013)
Kaempferol	Cytotoxicity, p21-dependent cell cycle arrest (G1 phase), inhibition of growth, and apoptosis induction	Rahman and Khan (2013)
Ent-kaurane	Cytotoxicity	Rahman and Khan (2013)
β-Lapachone	Inhibition of cell division cycle 25 (CDC25) phosphatases	Cragg and Newman (2005)
Lantadene A	Antiproliferative effect, caspase-3-dependent apoptosis, Bcl-2 downregulation, and Bax upregulation	Rahman and Khan (2013)
Leucocyanidin	Cytotoxicity, p21-dependent cell cycle arrest (G1 phase), inhibition of growth	Rahman and Khan (2013)
Liensinine	Cytotoxicity, p21-dependent cell cycle arrest (G1 phase), inhibition of growth	Rahman and Khan (2013)
Limonin	Antiproliferative effect	Hirano et al. (1994)
Liriodendrin	Inhibition of growth	Ran et al. (2013)
Liquiritigenin	Antiproliferative effect	Hirano et al. (1994)
Lupeol	Cytotoxicity	Rahman and Khan (2013)
Lunasin	Induction of apoptosis, inhibition H3 and H4 acetylation, and inhibition Rb protein phosphorylation	Rahman and Khan (2013)
Luteolin	Induction of apoptosis, inhibition H3 and H4 acetylation, and inhibition Rb protein phosphorylation	Rahman and Khan (2013)
Lycopene	Antiproliferation (cell cycle arrest, apoptosis induction) effect, anti-invasion, anti-metastasis	Ko and Moon (2015)

(continued)

Table 4.2 (continued)

Compound name	Mechanism of actions	References
Machicendiol	Antiproliferative effect	Hirano et al. (1994)
Machilin A	Antiproliferative effect	Hirano et al. (1994)
Magnolol	Antiproliferation (cell cycle arrest, apoptosis induction) effect	Millimouno et al. (2014)
Mahanine	Apoptosis induction	Rahman and Khan (2013)
Matairesinol	Antiproliferative effect	Hirano et al. (1994)
Methylcardols	Cytotoxicity	Kubo et al. (1993)
Mezerein	Induction of protein kinase C (PKC) activity	Saraiva et al. 2001.
Mollupentin	Cytotoxicity	Rahman and Khan (2013)
Morin	Anti-invasion and anti-metastasis effect	Ko and Moon (2015)
Myriceric acid B	Cytotoxicity, growth inhibition	Rahman and Khan (2013)
Myricetin	Apoptosis induction	Rahman and Khan (2013)
Myricetin-3-*O*-galactopyranoside	Apoptosis induction	Rahman and Khan (2013)
Naringenin	Antiproliferative effect	Hirano et al. (1994)
Neferine	Cytotoxicity, p21-dependent cell cycle arrest (G1 phase), inhibition of growth	Rahman and Khan (2013)
Nexrutine	Antiproliferation (cell cycle arrest, apoptosis induction) effect	Ko and Moon (2015)
Nitidine	Inhibition of topoisomerase I	Cragg and Newman (2005)
Nobiletin	Antiproliferative effect	Hirano et al. (1994)
Noscapine	Cell cycle arrest (G2/M phase) and induction of variety of cell death mechanisms including autophagy and mitotic catastrophe	Wang et al. (2012)
Nuciferine	Cytotoxicity, p21-dependent cell cycle arrest (G1 phase), inhibition of growth	Rahman and Khan (2013)
Nyctanthic acid	Cytotoxicity	Rahman and Khan (2013)
Oleanolic acid	Cytotoxicity	Rahman and Khan (2013)
Olomucine	Inhibition of cyclin-dependent kinases (CDKs)	Cragg and Newman (2005)

(continued)

Table 4.2 (continued)

Compound name	Mechanism of actions	References
Oridonin	Antiproliferation (cell cycle arrest, apoptosis induction) effect	Millimouno et al. (2014)
Panduratin A	Cell cycle arrest and apoptosis induction	Kirana et al. (2007)
Parthenolide	Antiproliferation (cell cycle arrest, apoptosis induction) and cytotoxicity effect	Millimouno et al. (2014)
Phytic acid (inositol hexaphosphate)	Cytotoxicity	Norhaizan et al. (2011)
Phloroglucinol	Apoptosis induction and caspase 3 and 8 activation	Kang et al. (2014)
Pinoresinol	Cytotoxicity and antiproliferative effect	López-Biedma et al. (2016)
Pseudolaric acid B	Antiproliferation (cell cycle arrest, apoptosis induction) effect	Millimouno et al. (2014)
Psoralen	Anti-metastasis	Ko and Moon (2015)
Pterostilbene	Antiproliferation (cell cycle arrest, apoptosis induction) effect	Ko and Moon (2015)
Quercetin	Cytotoxicity, p21-dependent cell cycle arrest (G1 phase), inhibition of growth	Rahman and Khan (2013)
Quercetin-3-*O*-galactopyranoside	Apoptosis induction	Rahman and Khan (2013)
Quercitol	Apoptosis induction, cell cycle arrest, downregulation of Bcl-2, Bcl-xL, survivin, IAP- 1, IAP-2, cyclin D1, and caspase-3 activation	Rahman and Khan (2013)
Remrefidine	Cytotoxicity, p21-dependent cell cycle arrest (G1 phase), inhibition of growth	Rahman and Khan (2013)
Resveratrol	Cell cycle arrest, and regulation of multiple cell signaling pathways	Wang et al. (2012)
Rohitukine	Cytotoxicity, cell cycle arrest (G2/M phase), caspase-activated apoptosis, growth inhibition through cyclin-dependent kinases (CDK2 and CDK1)	Rahman and Khan (2013)
Rosmarinic acid	Apoptosis induction, inhibition of growth and anti-metastasis activity	Hossan et al. (2014)
Sauchinone	Apoptosis induction	Ko and Moon (2015)
Sesamin (asarinin)	Antiproliferative effect	Hirano et al. (1994)
Silvestrol	Apoptosis induction	Kim et al. (2007)

(continued)

Table 4.2 (continued)

Compound name	Mechanism of actions	References
Silymarin	Cell cycle arrest, antiproliferation, induction of cyclin-dependent kinase inhibitors (p15, p21, and p27), downregulation of anti-apoptotic gene products (Bcl-2 and Bcl-xL), inhibition of cell survival kinases (AKT, PKC, and MAPK), and inhibition of inflammatory transcription factors (NF-kappaB), anti-invasion, anti-angiogenesis, and anti-metastasis	Agarwal et al. (2006)
β-Sitosterol	Cytotoxicity	Rahman and Khan (2013)
Stigmasterol	Cytotoxicity, p53 and Bax upregulation, Bcl-2 and survivin downregulation	Rahman and Khan (2013)
Sulforaphane	Cell cycle arrest associated with altered microtubule dynamic, cdc2 kinase activity, increased protein expression of cyclin B1, p21, and histone H1 phosphorylation	Wang et al. (2012)
Tehranolide	Antiproliferation (cell cycle arrest, apoptosis induction) effect	Ko and Moon (2015)
Thapsigargin	Apoptosis induction	Cragg and Newman (2005)
Thymoquinol dimethyl ether	Cytotoxicity	Rahman and Khan (2013)
Tinoscorside A	Antiproliferative effect	Rahman and Khan (2013)
Triptolide	Antiproliferative effect and apoptosis induction	Wang et al. (2012)
Umbelliferone	Apoptosis induction, cell cycle arrest, and DNA fragmentation	Yu et al. (2015)
Ursolic acid	Apoptosis induction and anti-metastasis effect	Ko and Moon (2015)
Verbascoside	Apoptosis induction and activation of HIPK2-p53 signaling pathway	Zhou et al. (2014)
Vinblastine	Inhibition of tubulin polymerization	Mans et al. (2000)
Vincristine	Inhibition of tubulin polymerization	Mans et al. (2000)
Wedelolactone	Antiproliferation (cell cycle arrest, apoptosis induction) effect	Millimouno et al. (2014)
Wogonin	Antiproliferative effect	Hirano et al. (1994)
Xanthorrhizol	Antiproliferation (cell cycle arrest, apoptosis induction), caspase activation, regulation of MAPK pathway, inhibition of Akt/NF-κB pathway	Oon et al. (2015)
Yakuchinone A	Apoptosis induction through the Bcl-2-mediated signaling pathway	Lin et al. (2013)

(continued)

Table 4.2 (continued)

Compound name	Mechanism of actions	References
Zeaxanthin	Cytotoxicity, apoptosis induction, decreased the expression of anti-apoptotic proteins (Bcl-2 and Bcl-xL) and increased the expression of pro-apoptotic proteins (Bak and Bax) and caspase activation (caspases 3 and 9)	Bi et al. (2013)
Zingerone	Inhibition of c-Jun N-terminal kinases (JNKs) signaling pathway	Bae et al. (2016)
Aplidine	Inhibition of growth, apoptosis induction, cytotoxicity, and inhibition of VEGF secretion	Broggini et al. (2003)
Aragusterol A	Cell cycle arrest	Mayer and Gustafson (2003)
Ascididemin	Apoptosis induction	Mayer and Gustafson (2003)
Bryostatin1	Antiproliferation	Mayer and Gustafson (2003)
Curacin A	Inhibition of tubulin polymerization	Wipf et al. 2004.
Discodermolide	Apoptosis induction	Mayer and Gustafson (2003)
Dolastatin10 and 15	Apoptosis induction, inhibition of microtubule assembly, anti-mitosis, induction of Bcl-2 phosphorylation	Amador et al. (2003)
Ecteinascidin 743 (ET743)	Regulation of transcription-coupled NER pathway	Takebayashi et al. (2001)
Fascaplysin	Inhibition of cyclin-dependent kinase 4 (CDK4)	Mayer and Gustafson (2003)
Indanone	Inhibition of VEGF expression	Mayer and Gustafson (2003)
Jaspamide	Induction of polyploidization	Mayer and Gustafson (2003)
Lyngbyabellin A	Disruption of cellular microfilaments formation	Mayer and Gustafson (2003)
Melophlins A and B	Reversal of transformed phenotype to normal	Mayer and Gustafson (2003)
Salinosporamide A	Proteasome inhibition	Macherla et al. (2005)
Spisulosine	Disassembly of actin stress fibers	Mayer and Gustafson (2003)
Theopederin A–E	Cytotoxicity	Fusetani et al. (1992)

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