Phytochemicals in the Prevention and Cure of Cancers

16

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Contents

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Abstract

Most of the early medicines relied on the prescription of specific plants and herbs for medications. This practice is still supported by the present-day research, because of the bioactive phytocomponents present in them. Acting as a defense barrier against several plant pathogens, including bacteria, viruses, and fungi, phytochemicals are also associated with the diminution of lethal diseases in humans, such as hypertension, diabetes, heart disease, etc., and can also effectively diminish the risks of developing certain cancers. Cancer is considered as a neoplastic disease, and despite advances in the modern medicine, it is still the fundamental cause of mortalities in developing as well as developed countries. Specifically, phytochemicals may act as antioxidants and/or nutrient protectors and inhibit the formation of carcinogens (cancer-causing agents) in the body. Furthermore, the potential benefits of phytochemicals as an anticancer agent also include improving the immune system, reducing inflammation, preventing DNA damage, and facilitating DNA repair, thereby slowing down cancer cell growth, regulating hormones, and preventing damaged cells from reproducing. The literature supports the fact that phytochemicals are advantageous, because of their safe, low-toxic, universal availability and their ability to synergize with chemotherapy and radiotherapy. Different studies suggest that regular intake of dietary phytochemicals is allied to low cancer risks. Thus, in this chapter, a summary of the therapeutic perspective of natural phytochemicals and cancer chemoprevention has been presented. Further, different mechanisms of cancer prevention using phytochemicals are discussed.

Keywords

Anticancer · Chemoprevention · Natural compounds · Phytochemicals · Anti-carcinogenic

Abbreviations

ACS	American Cancer Society
Akt	Protein kinase B
AML	Acute myeloid leukemia
AP-1	Activator protein-1
Bax	Bcl-2-associated X protein
Bcl-2	B-cell lymphoma 2
bFGF	Basic fibroblast growth factor
BTK	Bruton's tyrosine kinase
CDK	Cyclin-dependent kinases
c-myc	c-Myelocytomatosis
COX-2	Cyclooxygenase-2
CYP1A1	Cytochrome P450 family 1 subfamily A member 1
CYP1B1	Cytochrome P450 family 1 subfamily B member 1

DNA	Deoxyribonucleic acid
EGFR	Epidermal growth factor receptor
ERK2	Extracellular signal-regulated kinases 2
Fas/CD95	Apoptosis antigen 1 (cluster of differentiation 95)
GSTs	Glutathione S-transferases
HDACs	Histone deacetylases
HepG2	Human liver cancer cell line
HER2/neu	Human epidermal growth factor receptor-2
HIF-1α	Hypoxia-inducible factor-1α
HIV	Human immunodeficiency virus
HPV	Human papilloma virus
i.e.,	That is
ICD-O	International Classification of Diseases for Oncology
JAK2	Janus kinase 2
MAPK	Mitogen-activated protein kinase
MCF-7	Breast cancer cell line
MMP	Matrix metalloproteinase
mTOR	Mammalian target of rapamycin
NCDB	National Cancer Database
NF- κB	Nuclear factor-kappa B
PDGFR	Platelet-derived growth factor receptor
pHDACs	Pan-histone deacetylases
PI3K	Phosphoinositide 3-kinase
PKC	Protein kinases C
PPAR	Peroxisome proliferator-activated receptor
PTEN	Phosphatase and tensin homolog
pVHL	Van Hippel-Lindau tumor suppressor
Raf	Rapidly accelerated fibrosarcoma
Ras	Retrovirus-associated DNA sequences
Rb	Retinoblastoma
Skp2	S-phase kinase-associated protein 2
Src	Sarcoma
STAT3	Signal transducer and activator of transcription
Syk-ZAP-70	Spleen tyrosine kinase-zeta-chain-associated protein kinase 70
UV	Ultraviolet
VEGF	Vascular endothelial factor
VEGFR	Vascular endothelial growth factor receptor
WHO	World Health Organization
YPEL3	Yippee-like 3 gene

16.1 Introduction to Cancers

16.1.1 Definition and General Types of Cancer

The uncontrollable and abnormal growth of cells by disregarding standard rules of cell division leads to form cancers. Generally, signals for differentiation, division, or death are provided to the cells. But, cancer cells are independently against to these signals, and lead to abandoned growth and proliferation. It can be mortal if proliferation continues and spreads. Various studies articulate that nearly 90% of cancer-allied deaths are attributable to the spread of tumors. Thus, the progression is termed as metastasis (Kumar et al. 2015; Miller et al. 2016). Conferring to different types of cells human body resides, cancer types are distributed into five major categories, i.e., leukemia, carcinoma, lymphoma, myeloma, and sarcoma as well as spinal cord and brain cancers. Their distribution and subtypes are highlighted in Fig. 16.1. The classification chart has been compiled using data available on World Health Organization (WHO), International Classification of Diseases for Oncology (ICD-O) (https://codes.iarc.fr/).

16.1.2 Risk Factors of Cancer

Risk factors of cancer differ from types of cancer as well as the age of cancer patients. According to the National Cancer Database (NCDB) and the American Cancer Society (ACS) (https://www.cancer.org/) database, habitual or lifestyle-related factors, which increases risk of many different types of cancer include smoking, consumption of alcohol, unhealthy food, insufficient exercise, and being overweight. Environmental factors like exposure to different radon, air pollution, and radiations in the course of medical examinations or processes are also accountable in certain adult cancers. However, natural or artificial ultraviolet (UV) is shown to increase risks of skin cancers, including melanoma. These risks usually take several years of impact for cancer risk, so it can be reflected in adult age and not in children or teens, while childhood cancer treated with radiotherapy or chemotherapy can later acquire second cancer, specifically leukemia. Changes in DNA (inherited as well as acquired gene mutations) leads to relax suppressor genes or go for oncogenes that could also trigger cancer, whereas some of the cancers including cervical can be acquired by human papillomavirus (HPV) infections. In addition, risk of Kaposi sarcoma, Hodgkin lymphoma, and a few other cancers can be acquired by human immunodeficiency virus (HIV) infections (https://www.facs.org/quality-programs/cancer/ncdb/about).

16.1.3 Treatments of Cancer

Cancer can be treated by different means unrelated to the stages of cancer and the condition of patients. The traditional therapy includes radiotherapy, chemotherapy, immunotherapy, surgery, as well as targeted therapy (Njuguna et al. 2018). Various

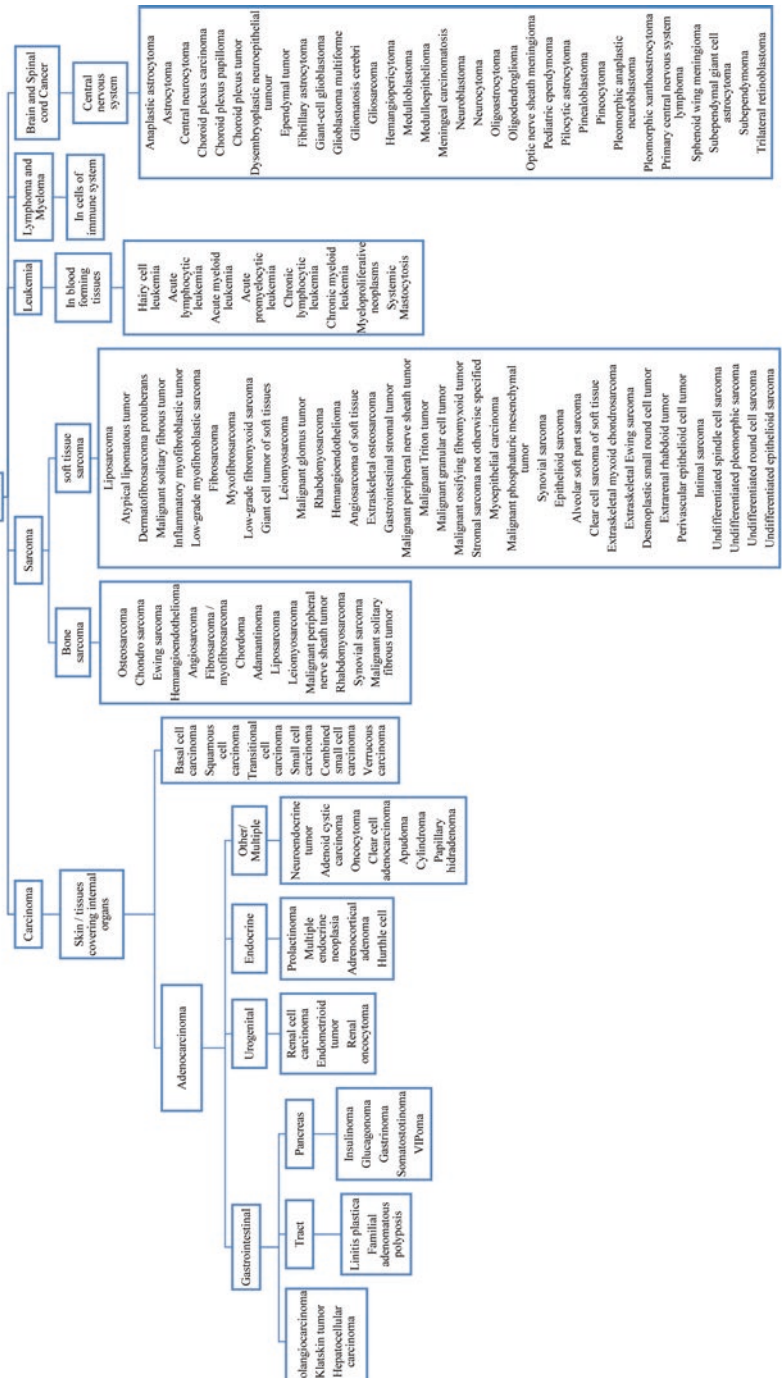

Fig. 16.1 General types and subtypes of cancer depending on different cell functions

new forms of treatments are also considered nowadays which depend on the information about clinical trials. These are deliberated as complementary and alternative therapies comprising photodynamic therapy, stem cell transplant, hyperthermia, donation and transfusion of blood, laser treatment, etc. (Miller et al. 2016; Njuguna et al. 2018).

16.1.4 Side Effects of Anticancer Drugs (Synthetic Drugs)

The most common side effects of anticancer drugs include vomiting, nausea, fatigue, infections (Ayoub et al. 2018), mouth problems, swelling, ostomies, pain, leg cramps (Baden 2015), fever, falling, sleep problems, seizures, eating problems, sweating, weakness, hiccups, changes in thinking or moods, prostheses, low blood counts, peripheral neuropathy, shortness of breath, urine or stool changes, lymphedema, sexual and fertility side effects, emotional side effects (depression, anxiety, distress) (El-Mowafy 2018), skin problems, dehydration (lack of fluids) (Ng et al. 2018), and hair loss (Wallisellen 2019). One of the synthetic anticancer drugs is doxorubicin, which is also effective against acute lymphoblastic leukemia and different breast, ovaries, and hepatocellular carcinomas. It is found that doxorubicin has harmful effects like cardiotoxicity which can lead to heart failure (Chen et al. 2011). Similarly, aspirin and celecoxib used for anticancer treatment caused some side effects like gastrointestinal bleeding, heart attack, and stroke (Cheng et al. 2016), whereas Panhistone deacetylases (pHDACs) inhibitors used as anticancer agent possess several side effects including taste disturbance, diarrhea, fatigue, weight loss, cardiac arrhythmias, bone marrow depression, and electrolyte changes (Prasad and Katiyar 2015). Few chemotherapy drugs, consisting of antimetabolites like methotrexate, hormones, molecular targeting agents, anti-tubulin agents like taxanes, and some DNA-interactive agents like cisplatin and doxorubicin are used for cancer therapy. However, these drugs are escorted with quite a few undesirable side effects like hair loss, bone marrow suppression, neurological problems, cardiotoxicity, and gastrointestinal injuries (Hosseini and Ghorbani 2015; El-Mowafy 2018; Wallisellen 2019). So researchers are hunting for some innovative anticancer agents from natural resources revealing insignificant side effects and enhanced efficacy.

16.2 Phytochemicals: Introduction and Different Mechanisms of Cancer Prevention by Phytochemicals

Phytochemicals are bioactive non-nutrient composites, originated in plants, and are responsible for the pigments, flavor, as well as fragrance of foods (Thomas et al. 2015). Over and above 5000 phytochemicals have been predicted in fruits, grains, and vegetables, while many of them are still unidentified (Hosseini and Ghorbani 2015). Phytochemicals positively affect human health via various mechanisms like signal transduction modulation, epigenetic modifications, regulating antioxidant properties, and modulation of metabolic pathways. Hence, phytochemicals have

comprehensively been studied for their anticancer potential through apoptosis, autophagy, angiogenesis, cellular differentiation, modulation of cancer growth, and its initiation with the aim of reducing side effects like nausea and fatigue (Tabolacci et al. 2019). Many studies have allied that intake of dietary phytochemicals has lowered the incidence of cancer by involving as safeguards in enhancing the repair of DNA, protecting by arming our antioxidant enzymes, and many more (Thomas et al. 2015).

Few plants, as well as phytochemical compounds, responsible for anticancer properties through some of the possible mechanisms are reviewed in this chapter and depicted in Fig. 16.2.

16.2.1 Through Antioxidant Activity

Compounds, inhibiting oxidation reaction that yields free radicals and leads to chain of reactions in order to damage cells are termed as antioxidants. Hence, these antioxidants are essential to maintain integrity of cells as well as homeostasis of the host immune system (Thyagarajan and Sahu 2018). Different antioxidants in foods, including phenols, flavonoids, carotenoids, curcumin, and nobiletin are recognized to be potent for the anti-carcinogenic property. The in vitro studies confirm that supplementing resveratrol- and flavonoid-rich fruits and vegetables in specific proportion lowered the rate of breast, prostate, and renal cancers (Bennett et al. 2012), while the carotenoid mixture helped to suppress hepatoma developed in liver cancer with a high risk as well as help to reduce breast cancer risk. Similarly, nobiletin and curcumin exhibited initiation of antitumor effects (Nishino et al. 2004). In another study, antioxidants like vitamin E and selenium reduced prostate and colon cancer risks. The study revealed that antioxidant vitamins and few phytochemicals help cancer cells to induce apoptosis and prevent angiogenesis as well as the spread of metastasis (Borek 2004). On the other hand, green leafy vegetables, fruits, and dietary quercetin also helped to reduce lung, breast, stomach, colorectal, and prostate cancer (Arsova-Sarafinovska and Dimovski 2013). In a similar way, 6-hydroxy-2,2-dimethyl-3-chrom, rosmarinic acid, 1-O-β-glucopyranosyl-1,4-dihydroxy-2-prenylbenzene, β-sitosterol 3-glucoside, and β-sitosterol isolated from methanol extract of *Gastrocotyle hispida* have shown potent antioxidant and anticancer property (Shahat et al. 2019).

16.2.2 Inhibition of Cellular Mechanisms

16.2.2.1 Cell Proliferation

A condition in which cell number increases, resulting in cell growth and cell division is called as cell proliferation. However, abnormal cell cycle results in accumulation of abnormal cells and its over-proliferation as well. This kind of abnormal and uncontrolled cell growth leads to distinct kinds of cancer (López-Sáez et al. 1998). So, inhibiting cell proliferation of abnormal cells as one of the cellular mechanisms is considered as one of the anticancer assets. It is revealed that polyphenols obtained from green tea also perform as chemopreventive mediators against prostate cancer by

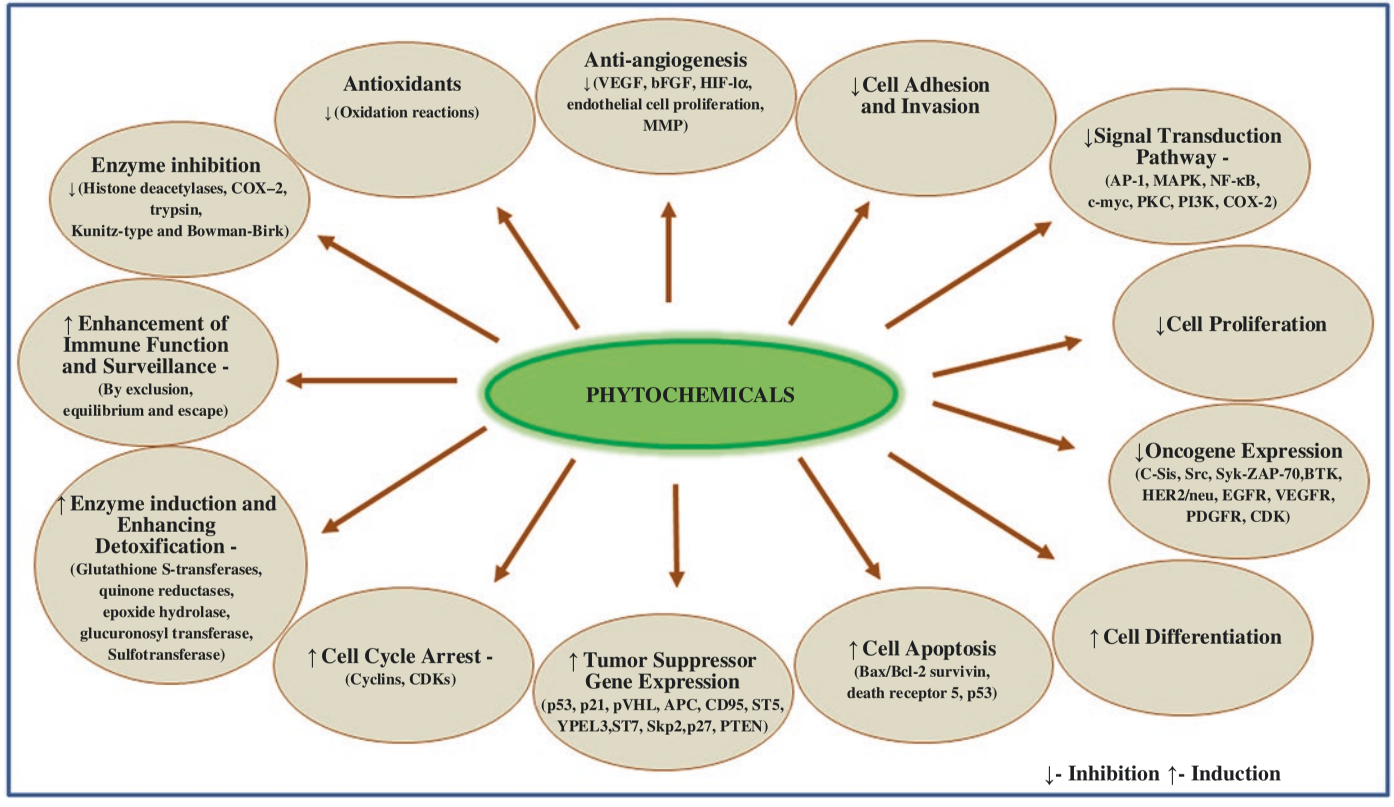

Fig. 16.2 Phytochemicals mediated anticancer potential through some of the possible mechanisms

inhibiting proliferation and inducing apoptosis in cell cultures (Adhami et al. 2004), while methanolic extract of *Oxygonum sinuatum* inhibited proliferation and migration of mammalian endothelial cell (Njuguna et al. 2018). Moreover, anticancer potential of daily diet phytochemical ingredients like curcumin, sulforaphane, lycopene, plus quercetin was studied in colon epithelial as well as cancer cells. Studies here examined mitochondrial activity, DNA synthesis, and lactate dehydrogenase release tests, which are found to inhibit proliferation of colon cancer cell besides not harming the normal colon epithelial cells (Langner et al. 2019), whereas microtubule-targeting agents revealed inhibition potential of the proliferation of cancerous cells. The first group of antimitotic agents was paclitaxel and vinca alkaloids which revealed the capability to inhibit proliferation of cancerous cell (Mukhtar et al. 2014). In a similar way, phytochemicals like vincristine and vinblastine when treated to patients with acute lymphocytic leukemia, testicular cancer, as well as Hodgkin's lymphoma successfully inhibited cell proliferation. Similarly, flavopiridol, fangchinoline, 5,3′-dihydroxy-3,6,7,8,4′-pentamethoxyflavone, isorhamnetin, resveratrol, silymarin, and indole-3-carbinol also inhibited proliferation of numerous cancerous cells including colon, breast, kidney, pancreas, prostate, head/neck, endometrial, leukemia, lung, colorectal, bladder, myeloma cancer cell lines, and various other human tumor cells (Bailon-Moscoso et al. 2017).

16.2.2.2 Cell Adhesion and Invasion

A process in which cells form contact with each other or with their substratum through specialized protein complex is called as cell adhesion (Oh et al. 2012), whereas cell invasion is related to cell migration and navigation through extracellular matrix within tissues or to infiltrate neighboring tissue (Pavese et al. 2010). For cancer, adhesion and invasion are the shortest extension and penetration by cancer cells into neighboring tissue for the formation of metastasis. So, inhibiting adhesion and invasion mechanism of cancer cells can be considered as one of the key steps in cancer chemoprevention therapy. Fisetin from strawberries and apples, curcumin from *Curcuma longa* L., and rosmarinic acid found in various medicinal herbs including, thyme, lemon balm, rosemary, sage, oregano, peppermint, as well as culinary spices revealed inhibition potential of cell adhesion, migration, and invasion with variations in their dosages (Wang et al. 2012). Here, curcumin also revealed anticancer property by downregulating the transcription factors, repressing genes responsible for cell adhesion molecules, as well as by decreasing metastasis (Rahmani et al. 2014). Similarly, thymoquinone isolated from seeds of *Nigella sativa* showed anti-metastatic potential by inhibiting cell invasion, cell migration, cell adhesion, and cytoskeletal reorganization when studied on human renal carcinoma cell (Liou et al. 2019), while garlic contains diallyl trisulfide as organosulfur compound reduced matrix metalloproteinase-2 and metalloproteinase-9 (MMP-2 and MMP-9) expressions along with the inhibition of melanoma cell invasion and migration in humans. Here, diallyl trisulfide also disrupted the integrin signal pathways and henceforth inhibited adhesion (Wang et al. 2017). In a similar way, gallic acid, carnosol, caffeic acid, capsaicin, chlorogenic acid, 6-gingerol, 6-shogaol, and their resultant derivatives were proposed to have anti-invasion and anti-metastasis potential (Weng and Yen 2012). In the context of plant extracts,

Porphyra tenera extracts were responsible for inhibition of cell adhesion, migration, and cell invasion in human hepatoma cancer cells. Here, the extracts eventually inhibited gelatinase-A/-B activities (MMP-2/ MMP-9) as well as increased tissue inhibitors of MMP-1/-2 expression by showing anti-metastatic exploit (Do Thi and Hwang 2014), whereas in human lung squamous carcinoma cells, tannin fractions of *Fructus phyllanthi* were responsible for inhibition of cell migration and invasion showing decrease in MMP expressions through regulation of mitogen-activated protein kinases (MAPK) pathway (Zhao et al. 2015). Likewise, root extracts of *Withania somnifera* used in even a small concentration have the potential for inhibition of breast cancer metastasis showing minimal antagonistic properties in rats (Yang et al. 2013).

16.2.2.3 Signal Transduction Pathways

A process in which molecular signals are transmitted from outside to inside the cells is called signal transduction. Generally, these signals affect different functions of cells like cell division as well as cell death. But, cells with permanent changes in signal transduction molecule may form cancer (Liem et al. 2002). So, inhibiting these signals in cancer cells can promote the killing of the cancer cell. Hence, the search for inhibitors of signal transduction pathway could be one of the therapeutic approaches in cancer treatment. The core targets for inhibiting signal transduction pathways are activator protein-1 (AP-1), MAPK, NF-κB, c-myc expression, protein kinases C (PKC), phosphoinositide 3-kinase (PI3K), as well as abnormal cyclooxygenase-2 (COX-2) (Gupta et al. 2017). Ginger consisting of 10-gingerol and 6-gingerol component showed potency to control PI3K/Akt pathway signal transduction which links to anticancer property, whereas sulforaphane found in cruciferous vegetables studied on ovarian cancer cell lines showed an appropriate reduction in PI3K. It also activated phosphorylated levels of Akt and Akt proteins (Suvarna et al. 2017). Similarly, apigenin in endometrial cancer cells has shown particular actions on AP-1 to regulate MAPK pathway, whereas coumarin showed involvement in downregulating pathways like NF-κB, MAPK, as well as Akt. While in combination with paclitaxel, it encouraged a synergistic reduction in the occurrence of the tumor as well as tumor volume when studied in mice (Farrand et al. 2014). However, curcumin, cyanidine, rosmarinic acid, sulforaphane, triterpenoids, resveratrol, and tocopherols were found to inhibit or suppress the activity of COX-2 gene expression in various cancers (Wang et al. 2012; Gupta et al. 2017). Also, in vitro and in vivo trials demonstrated catechol to inhibit c-myc phosphorylation in mice suffering from lung cancer (Lim et al. 2016). Additionally, eugenol found in cloves, bay leaves, nutmeg, cinnamon, and basil showed potential to downregulate the c-myc expression (Ng et al. 2018). Later, in vitro and in vivo studies for anticancer potential carried out using quercetin in combination with cisplatin showed inhibition of the PKC pathway (Purnamasari et al. 2019). Some phytochemicals like benzyl isothiocyanate, genistein, thymoquinone, silibinin, epigallocatechin gallate, parthenolide, naringenin, isoliquiritigenin, ginsenosides, and sulforaphane also suppressed breast carcinoma by several signaling transduction pathways (Younas et al. 2018).

16.2.2.4 Oncogene Expression

Gene responsible to cause cancer is called an oncogene, while a normal gene is a proto-oncogene that may turn to oncogene due to increase in expression or mutation. Generally, these proto-oncogenes code for proteins which regulates cell differentiation and their growth (Croce 2008). So, inhibition of oncogene expression or suppression of proto-oncogene expression using phytochemicals can also help in cancer chemoprevention. Basically, oncogenes are classified in six different categories

1. Cytoplasmic tyrosine kinases including different families (like Src, Syk-ZAP-70, BTK family of tyrosine kinases, and Ab1 gene in chronic myeloid leukemia).
2. Growth factor or mitogens (C-Sis).
3. Receptor tyrosine kinases (including human epidermal growth factor receptor 2 (HER2/neu), epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR), and platelet-derived growth factor receptor (PDGFR)).
4. Cytoplasmic serine/threonine kinases (including Raf kinases and cyclin-dependent kinases (CDK)).
5. Regulatory GTPases (including Ras proteins).
6. Transcription factors (including myc gene, erb A, jun, ets, fos, and myb) (Croce 2008).

Flavonoids inhibiting oncogene expressions were classified based on their activities on cancer cells. Some of them are particularized here. Flavones like luteolin interfered in JNK, p38, and Akt signaling pathways and led to induce programmed cell death along with autophagy in ANA-1 cells. It also showed the potential to inhibit beclin-1 and Bcl-2 together with activation of caspase-3 and -8, while flavonols like galangin induced apoptosis-targeted signals like Akt/PI3K/mTOR resulting in inhibition of cell proliferation in human kidney cancers. However, flavononols like taxifolin inhibited mammary carcinogenesis in LXR-mTOR/Maf1/PTEN and CYP1A1- and CYP1B1-mediated cancers. Similarly, flavans like catechin inhibit programmed cell death ligand 1 to treat lung tumor. Anthocyanidins like delphinidin when studied in human osteosarcoma cell lines showed interference in ERK2/p38MAPK pathway to promote apoptosis and epithelial-mesenchymal transition process (Chirumbolo et al. 2018). A preceding study discussed five phytochemicals, namely, epigallocatechin gallate, kaempferol, genistein, morin, and caffeic acid phenethyl ester for their role in cancer remedy through modulating coding as well as non-coding genes. Some of them are elaborated here. Epigallocatechin gallate showed potency to inhibit expression of neurogenic locus notch homolog protein 2 along with transcription factor HES1 in colorectal cancer and can also target Ras-GTPase-activating protein-binding protein 1 which have chemopreventive effects in lung cancer. Also, kaempferol via downregulating c-myc helps to stimulate ovarian cancer cell apoptosis and can promote the cause of cellular death by reducing Bcl-2 expression and increasing Bax expressions, while genistein helps to target some intermediary signaling pathways like Akt, NFκB, Wnt, and p53 to modulate antitumor activities. Similarly, morin when targeted to Bax, Bcl-2, and cytochrome c in

human leukemia cells showed caspase-dependent apoptosis by means of the intrinsic pathway. Likewise, caffeic acid phenethyl ester targets the NFκB transcription factor to promote programmed cell death in various cell lines (Budisan et al. 2017). Moreover, capsaicin was responsible for the transformation of phenotype in H-ras MCF-10A cells and inhibiting its growth with time-dependent activation of p38 and c- Jun N-terminal kinase-1 along with deactivating ERK-1 and ERK-2, resulting in induction of apoptosis via caspases-3 and fragmentation of DNA. Similarly, rocaglamide as leukemia (Jurkat T, AML) cells treatment showed interference in the intrinsic death pathway by modulating MAPK activities and thereby showing the induction of apoptosis (Kaur et al. 2018). In a similar way, gingerols, emodin, ginsenoside RG3, honokiol, parthenolide, triptolide, wogonin, thymoquinone, resveratrol, andrographolide, quercetin, apigenin, and many more phytochemicals have conferred their ability to inhibit PI3K pathways targeting Akt in several human cancers (Suvarna et al. 2017).

16.2.3 Induction of Cellular Activities

16.2.3.1 Cell Differentiation

A progression in which cells become specialized so as to perform specific functions including neuron, liver cells, or blood cells is referred to as cell differentiation, whereas in cancer, well-defined cancer cells appear more similar to that of normal cells and tend to spread and grow slower than that of undifferentiated cancerous cells. Here, a differentiation term differs for respective types of cancers (Yan and Liu 2016). Hence, drugs inducing differentiation are deliberated as one of the promising lines of attack in cancer treatment. In this regard, all-trans retinoic acid (also called tretinoin), one of the anti-acne medications also used for acute promyelocytic leukemia, was found to induce differentiation in various types of cells and thus effectively used in cancer prevention and treatment (Liu et al. 2015). Similarly, compounds like hydroxyzine, promethazine, levomepromazine, and buclizine were responsible for inhibition of cancer cell growth via direct binding to the translationally controlled tumor protein expression and inducing the cell differentiation of leukemia cells and breast cancer (Seo et al. 2017). In a similar manner, natural phenol resveratrol from peanuts, red grapes skin, and other fruits when studied in human promyelocytic leukemia induced cell differentiation and thus possessed cancer chemopreventive potential (Wang et al. 2012), while a natural isoflavon, i.e., genistein, found in *Genista tinctoria*, soybeans, chickpeas, and other legumes promotes melanoma cell differentiation by stabilizing protein-linked DNA strand breakage as well as by inhibition of angiogenesis (Ng et al. 2018). Moreover, methanolic extract of *Biophytum sensitivum* Dc plant when tested on Ehrlich ascites carcinoma cells and Dalton's lymphoma ascites showed increased count of white blood cells and bone marrow cells along with enhancement of stem cell differentiation (Manisha and Kumar 2018). Additionally, fish oil fats also considered as food phytochemicals were found to increase colon cell differentiation rates (Ferrari 2004).

16.2.3.2 Cell Apoptosis

Cell apoptosis means cellular suicide. It is also mentioned as a process of programmed cell death or self-destruction of cells. Cell necrosis is the premature death of living tissues and cells (Wong 2011). Here, flaws in mechanisms of physiological apoptosis or necrosis contribute to unrestrained cell expansion leading to the progression and development of cancer. So, inducing cell apoptosis or necrosis is an utmost important strategy in cancer therapy. The chief polyphenol catechin called epigallocatechin-o-gallate isolated from green tea extract (*Camellia sinensis*) interfering in cyclic guanosine monophosphate-dependent pathway or acid sphingomyelinase pathway in chronic myeloid leukemia cells played a crucial role to induce cellular death providing anticancer properties (Huang et al. 2015). Hence, epigallocatechin-o-gallate can be useful for the treatment of bladder, cervical, brain, and prostate cancer (Wang et al. 2012). Similarly, the essential oil obtained from *Myrtus communis* L. revealed cytotoxic activity by apoptosis mechanism thereby suggesting it as a natural anticancer compound, while a compound myrtucommulone derived from leaves of *M. communis* revealed increased caspases 3 and 9 activities. It also further released nucleosome in cytochrome c as well as cytosol from mitochondria resulting in DNA fragmentation cleavage along with poly-ADP-ribose polymerases associated with cell apoptosis (Harassi and Ajouaoi 2019). Likewise, curcumin found in turmeric when administered in human lung cancer cells induced apoptosis. Studies also revealed that curcumin helps to induce death in pancreatic adenocarcinoma cells and reduce numerous apoptosis inhibitors (Radhakrishna Pillai et al. 2004; Díaz Osterman et al. 2016). However, a triterpene like-cucurbitane called as 3β,7β-dihydroxy-25-methoxycucurbita-5,23-diene-19-al found in *Momordica charantia* (a wild bitter gourd) helped to induce autophagy and apoptosis in breast cancer cells via peroxisome proliferator-activated receptors (PPAR)-γ (Weng et al. 2013). Phytochemicals of *Allium sativum* clinically tested in colorectal and pancreatic cancer patients increased number and activity of natural killer cells (Hosseini and Ghorbani 2015), whereas saffron a rich carotenoid includes two major components, i.e., crocin and crocetin. According to the in vitro, in vivo and preclinical facts, saffron and its constituents when consumed in daily diet revealed antitumor potential (Bhandari 2015), while saffron isolated from *Crocus sativus* L. exhibited apoptotic and cytotoxic induction in lung cancer cells (A549) (Samarghandian et al. 2013). Two different concentrations (i.e., 0.1% and 1%) of *Thymus vulgaris* L. extract were studied in vivo and in vitro against breast carcinoma. Both doses showed a significant decrease in the mitotic activity index. Moreover, the 4 T1 (breast cancer cell line derived from mammary gland tissue of mice) necrosis/tumor area was reduced to 85% and 84% by treatment with 0.1% and 1% of extract, respectively, as compared to the control rat models. Additionally, the 1% extract reduced the frequency of tumors by 53% in comparison to control (Kubatka et al. 2019). Similarly, anticancer potential of fruit and leaf extracts of *Ficus carica* studied in Huh7it cells revealed the occurrence of necrosis and apoptosis at a high percentage in the presence of leaf extracts (Purnamasari et al. 2019). Also, various mechanisms like apoptosis, cytotoxicity, autophagy, and interference with signaling pathways were observed in the presence of *Piper nigrum* revealing anticancer potential against colon, prostate, cervical, and breast cancer cell lines (Takooree et al. 2019).

16.2.3.3 Tumor Suppressor Gene Expression

Tumor suppressor genes are mentioned as normal genes with the ability to repair DNA, delay cell division, or decide cell death. When the tumor suppressor gene loses the ability to work in a proper way, cells grow in an uncontrolled manner which later forms cancer (Guo et al. 2014). So, inducing expression of tumor suppressor genes may possibly be beneficial in cancer therapy. The first tumor suppressor gene discovered is the retinoblastoma (Rb) gene followed by pVHL, APC, CD95, ST5, YPEL3, ST7, ST14, Skp2, p27, PTEN, and one of the most important ones being the p53 gene (Osborne et al. 2004). Recent reports suggest that phytochemicals induce the expressions of tumor suppressor genes. In this regard, luteolin, a flavonoid, induced Fas/CD95 expression and activated caspase-8 in HLF hepatoma cells. It was also observed that luteolin has the ability to decrease Tyr phosphorylation of STAT3 (which is recognized to act as a negative regulator of Fas/CD95 transcription) and increase the expression of Fas/CD95 (Imran et al. 2019). Curcumin from turmeric has potential to control the progression of tumor cells by inducing tumor suppressor pathways p53 and p21. It also upregulates p16 and numerous other tumor suppressors, JAK2 and STAT3 pathway inhibition, which leads to decrease in smooth muscle actin and migration/invasion capability of breast cancer-associated fibroblasts (Wang et al. 2012; Younas et al. 2018). However, kaempferol from tea, broccoli, and grapefruit interferes in the intrinsic pathway and activates p53 to induce apoptosis in the ovarian cancer cell. Later, kaempferol also proved to induce PTEN expression and Akt inhibition in bladder cancer (Wang et al. 2012; Budisan et al. 2017). Induction of p53, as well as inhibition of STAT3 and NF-κB, was observed due to apigenin in HER2-overexpressing MCF-7 breast carcinoma cells by extrinsic pathway (Younas et al. 2018). In another recent study, it was found that the major component of *Ficus carica* quercetin when individually treated with HepG2 liver cancer cells reported to stabilize p53 and increase Bax/Bcl-2 ratio leading to apoptosis (Purnamasari et al. 2019).

16.2.3.4 Cell Cycle Arrest

A situation when the cell detects any defects or any damage that occurs in DNA, an arrest occurs through several mechanisms to delay or halt the cell cycle. In cancer cells, genetic mutations occur which leads to regulatory malfunctioning and uncontrolled cell proliferation (Rastogi and Mishra 2012). Hence, induction of cell cycle arrest in cancer cells using phytochemicals may be considered as another cancer therapy strategies. In this context, various experimental and preclinical procedures proved that tea flavonoids containing epigallocatechin-3-gallate possess a key role in different cancer treatments via inducing cell cycle arrest (Gödeke et al. 2013). In addition, ethyl acetate extract of *Annona muricata* leaves showed cell cycle arrest in G1 phase associating antiproliferative effect and induced apoptosis through mitochondria-mediated pathway when studied against colon and lung cancer cells individually (Zorofchian Moghadamtousi et al. 2014). Studies based on breast cancer cell lines show that different phytochemicals help to promote cell cycle arrest in different ways. Few of them includes ginsenoside Rg5, a-mangostin, apigenin, isoliquiritigenin, sulforaphane, and curcumin. Here, apigenin has the potential of

inducing cell cycle arrest by suppressing CDK-1, cyclin A, and B that are important for G2 to M phase transition in the cell cycle, while ginsenoside Rg5 helped arrest at G0/G1 phase of the cell cycle by upregulating p21, p53, as well as p15 and down-regulating CDK-4, cyclin E2, and cyclin D1in breast cancer cell lines. Additionally, curcumin along with folic acid enhanced arrest at the G2/M phase of the cell cycle (Younas et al. 2018), while prostate cancer cells treated with caffeic acid phenethyl ester regulated the expression of Skp2, p21, p53, Cip1, as well as p27Kip1 genes leading to induction of cell cycle arrest and inhibition of cell growth (Budisan et al. 2017). Similarly, several mechanisms like activating p53, cell cycle arrests in G0/G1 phase and S phase were triggered by quercetin in leukemia and colorectal carcinoma, respectively. Additionally, G2/M phase arrest was also triggered by quercetin in breast cancer, esophageal cancer, as well as leukemia cells (Purnamasari et al. 2019). Moreover, the aqueous extract of white coca tea to treat human prostate cancer cells revealed cell cycle arrest in G2/M phase when studied in vitro and in vivo, while isoquercetin in addition to silymarin blocked G1 phase of the cell cycle when studied in human liver cells as well as G1/S phase when studied in prostate, ovary, colon, bladder, lung, and breast tumor cells. Similarly, propolis arrested S/G2 phase of cell cycle and inhibited the growth of tumor (Bailon-Moscoso et al. 2017). In a similar manner, sugiol, oridonin, honokiol, gallic acid, and indole-3-carbinol arrest cell cycle in the human breast, prostate, colon, and other different cancerous cell lines (Kaur et al. 2018), while lycopene induced arrest at G0/G1 phase of cell cycle and/or accumulated at S phase in colon cancer cells. Moreover, a recent study shows the synergistic effect of a cocktail containing resveratrol, genistein, C-phycocyanin, indol-3-carbinol, curcumin, and quercetin-induced cell cycle arrest in breast cancer (Langner et al. 2019).

16.2.4 Other Mechanisms

16.2.4.1 Enzyme Induction and Enhancing Detoxification

Generally, enzymes help to accelerate the chemical reaction in the body and participate in many cell functions including cell signaling, growth, and division. Hence, induction of enzymes activity through phytochemicals is one of the trending approaches towards cancer therapy. Therefore, glutathione S-transferases (maintain integrity of cells and protect against DNA damage through catalyzing conjugation of glutathione), quinone reductases (the enzymes present in cells that make certain molecules less toxic), epoxide hydrolase, glucuronosyl transferase (catalyzes broad range of glucuronidation of xenobiotic along with endogenous compounds), and sulfotransferase (enzymes that catalyze sulfonation) are few enzymes involved in phase II metabolism and induced by some phytochemicals or its bioactive compounds which are highlighted below (Dellinger et al. 2012; Abdull Razis et al. 2014; Schnekenburger et al. 2014). Camptothecin can be obtained from numerous plants including *Canzptotheca acirminata* and *Mappia foetida* that have the potential to target topoisomerase I (enzymes involved in DNA supercoils relaxation) to contribute to antitumor activity. Similarly, compounds like 20-(S)- camptothecin and

20-(S)-9-nitrocamptothecin have antitumor potential when studied in prostate cancer, melanoma, cholangiocarcinoma, breast carcinoma, and ovarian carcinoma, while curcumin decreased lymphocytic GSTs activity (family of phase II detoxification enzymes) (Hosseini and Ghorbani 2015). Moreover, phytochemicals present in vegetables including spinach, leaf lettuce, broccoli, cabbage, cauliflower, Brussels sprouts, green beans, carrots, celery, ginger, green onions, leeks, and asparagus as well as compounds isolated from them like butylated hydroxyanisole, benzyl isothiocyanate, allyl sulfide, and dimethyl fumarate induced enzymes like GSTs, quinone reductase, and related detoxification systems followed by activating apoptosis in human colon carcinoma cells (Kirlin et al. 1999). In addition, alantolactone found in medicinal plants like *Inula racemosa*, *Inula helenium L., Inula japonica, Radix inulae,* and *Aucklandia lappa* was observed to induce detoxifying enzymes by activating PI3K and JNK signaling pathways (Millimouno et al. 2014). Similarly, phenethyl isothiocyanate, isolated from cruciferous vegetables such as watercress, modulated carcinogen-metabolizing enzyme systems. Here, phenethyl isothiocyanate induced sulfotransferase, glucuronosyl transferase, and epoxide hydrolase levels when studied in mice (Abdull Razis et al. 2014). However, UDP-glucuronosyl-transferase family of enzymes also showed the potential of detoxification of carcinogens along with clearance of anticancer drugs (Dellinger et al. 2012). Likewise, limonene and sobrerol increased phase II enzyme activities and prohibited carcinogenesis initiation in rat with breast cancer (Bruno and Njar 2007).

16.2.4.2 Enzyme Inhibition

Enzyme inhibition is a concept where the action of an enzyme is blocked. Thus, phytochemicals acting as enzyme inhibitors may block certain enzymes that are required for the cancer cell to grow. Histone deacetylases inhibitors are helpful to induce phenotypes in different transformed cells like growth arrest, mitotic cell death, apoptosis, and reactive oxygen species-assisted cell death. Here, green tea polyphenols containing a mixture of epicatechin monomers inhibited the growth of histone deacetylases activity and induced death of melanoma cells (Prasad and Katiyar 2015), while isothiocyanates, sulforaphane, and erucen phenylhexyl isothiocyanates are potent histone deacetylases inhibitors in prostate, lung, pancreatic, and bladder cancer therapy (Mitsiogianni et al. 2019). Similarly, phytochemicals like quercetin, apigenin, curcumin, indirubin, isothiocyanates, butyrate, and baicalin and baicalein (obtained from *Scutellaria baicalensis*) were reported as histone deacetylases inhibitors for anticancer therapy (Evans and Ferguson 2018). Likewise, COX-2 enzymes (convert arachidonic acid to prostaglandins) are found to be overexpressed and upregulated in many cancers. In this perspective, curcumin was found to act as COX-2 inhibitors in cell lines of colon cancer and inhibited critical stage of tumor initiation (Rahmani et al. 2014), while other compounds like tocopherols, tocotrienols, phytosterols, pterostilbene, piceatannol, and resveratrol showed their efficacy as COX-2 inhibitors (Soldati et al. 2018). Additionally, plant protease inhibitors also show their applicability in cancer therapy and have been reviewed by several authors. In this regard, protease inhibitors present in *Cicer arietinum* L as well as *Bauhinia* seeds (rich in serine and cysteine) inhibited cell viability in

prostate cancer and breast cancer, whereas *Enterolobium contortisiliquum* trypsin inhibitor blocked the activity of trypsin, plasmin, chymotrypsin, and kallikrein which leads to inhibit cell adhesion, invasion, as well as migration in gastric cancer. Moreover, seeds of *Glycine max* possess both Kunitz-type inhibitors and Bowman-Birk inhibitors which are helpful in colorectal, colon, prostate, ovarian, and breast cancers, whereas black-eyed pea trypsin/chymotrypsin inhibitor induced apoptosis in breast cancer cells (Srikanth and Chen 2016).

16.2.4.3 Enhancement of Immune Function and Surveillance

The situation when the immune system identifies and removes the cancerous cells is called immune surveillance (Cook et al. 2018). The immune system works for cancer cell removal by three steps, i.e., exclusion (elimination), equilibrium, and escape. In the exclusion type of mechanism, identification and destruction of cancer cells is taken care by the immune system. In the equilibrium type of mechanism, cancer cells are wiped out completely by the immune system. In escape type of mechanism, the immune system is helpless in controlling the proliferation of cancerous cells and hence unable to eradicate tumor (Nouroz et al. 2016). Numerous phytochemicals like isothiocyanates, genistein, lycopene, curcumin, and glucosinolates are reported to aid the regression of tumors in a few clinical trials. Furthermore, boosting the immune system was claimed by phytochemicals like flavonoids, zinc, vitamin C, and omega-3 fatty acids (Vinay et al. 2015). Some of the reviews articulate that inhibitors of the CDK-4 and CDK-6 in cancer cells were initially designed to inhibit cell cycle progression and its proliferation. But these inhibitors of CDKs proved to have an indirect effect in activation of immune surveillance. So, CDK inhibitors further studied found phytochemicals like flavopiridol, glycyrrhizin, rosamultic acid, proanthocyanidins, berberine, isoliquiritigenin, resveratrol, propolis, nar (flavanone), and indole-3-carbinol have potential role in anticancer chemotherapeutics (Bailon-Moscoso et al. 2017; Chaikovsky and Sage 2018). Enhancing natural killer cells is one of the approaches to destroy tumor by perforin and granzyme that are essential for tumor cell death as well as immune surveillance. One of the important roles of natural killer cells is to kill virally infected and cancerous cells. Phytochemicals found in *Agaricus blazei* teas, *Andrographis paniculata*, *Ganoderma lucidum*, nitrogenated soy extract, as well as natural products like ascorbic acid, immune modulator mix, transfer factor plus, selenium, and vitamin E helped to control cancer by enhancing the natural killer cells efficiency (Latorre et al. 2014; Nouroz et al. 2016). Similarly, resveratrol, polyphenols present in tea like epicatechin-3-gallate and epigallocatechin-3-gallate, improved elimination of transformed cells and enhanced innate immune surveillance (Kotecha et al. 2016). Some medicinal plant extracts or phytochemicals show promising cancer immunotherapeutic properties with different strategies and are discussed in several reviews. A recent review discusses that shikonin and hypericin helped to enhance tumor vaccine efficacy to induce immunogenic cell death in melanoma and orthotopic high-grade glioma mice models, respectively. Similarly, *Astragalus membranaceus*, *Codonopsis pilosulae*, and *Dioscorea alata var. purpurea* extract as well as polysaccharides from *Ganoderma lucidum*, *Anoectochilus formosanus*, and *Schisandra*

chinensis showed specific immune cell activation or cell-based vaccine immunity potential in the tumor microenvironment in carcinoma tumor, lung cancer patient, and melanoma mice tumor models. Moreover, artemisinin, paclitaxel, isothiocyanate, berberine, mistletoe extract, green tea extract, broccoli, resveratrol, curcumin, noscapine and its derivatives, and piperine were responsible to suppress oxidative stress in the tumor microenvironment (Yin et al. 2017).

16.2.4.4 Anti-Angiogenesis

Formation of new blood cells/vessels is termed as angiogenesis. It involves growth, differentiation, and migration of endothelial cells. Generally, tumor cells also need blood nutrients for their growth. So, chemical signals are sent by tumor cells to stimulate blood vessel growth by which it carries blood to the tumor. But, angiogenesis inhibitors (also called as anti-angiogenesis) block the nutrients and allow tumors and destroy circulating pathway for tumor cells which leads to its starvation. Hence, these angiogenesis inhibitors are important in cancer treatment (Nishida et al. 2006). Angiogenesis can be modulated by several steps such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), hypoxia-inducible factor-1α (HIF-1α) signaling pathway, endothelial cell proliferation, as well as migration or MMP activity (Mirossay et al. 2018). Quercetin, cardamonin, kaempferol, luteolin, licochalcone E, rhamnazin, paxillin, epigallocatechin-3-gallate, barbigerone, galangin, myricetin, licochalcone A, chrysin, hispidulin, nobiletin, panduratin A, naringenin, xanthoangelol, xanthohumol, isoxanthohumol, eupatorin, butein, delphinidin, isoliquiritigenin, neoisoliquiritigenin, hydroxy safflower yellow A, 4′-acetoamido-4-hydroxychalcone, 1,3-diphenyl-propenone, 4-hydroxychalcone, artemisinin, taxifolin, allyl isothiocyanate, (E)-2-(4′-methoxybenzylidene)-1-benzosuberone, resveratrol, and wogonin repressed VEGF signaling pathway either because of direct effect on VEGF/VEGFR2 or by modulating VEGFR2-mediated downstream signaling. Also, chrysin, a 5,7-dihydroxyflavon, luteolin, and apigenin were found to inhibit the interleukin-6 (IL-6) pathway, while nobiletin, kaempferol, alliin, hydroxy safflower yellow A, emodin, 4-hydroxychalcone, and genistein were responsible to inhibit bFGF signaling pathway. Similarly, wogonin, astaxanthin, isoliquiritigenin, neoisoliquiritigenin, epigallocatechin-3-gallate, theaflavin-3,3′-digallate, combretastatin, oleuropein, γ-tocotrienol, nobiletin, flavopiridol, curcumin, and caffeic acid were responsible to inhibit HIF-1 signaling pathway. In addition, quercetin, xanthohumol, isoxanthohumol, curcumin, isoliquiritigenin, neoisoliquiritigenin, butein, chrysin, kaempferol, 3-hydroxyflavon, astaxanthin, nobiletin, wogonin, luteolin, thymoquinone, panduratin A, hydroxy safflower yellow A, piperine, zerumbone, myricetin, and epigallocatechin-3-gallate were found to inhibit different MMPs, specifically MMP-2 and MMP-9 (Jeong et al. 2011; Ean Jeong Seo 2013; Mirossay et al. 2018; Younas et al. 2018; Rajasekar et al. 2019).

16.3 Conclusions and Future Prospects

Unlike chemotherapeutic drugs, phytochemicals are meddling with all three stages of carcinogenesis, i.e., initiation, promotion, or progression, for protection against cancer. In addition, these phytochemicals also show a synergistic effect when used with chemotherapy medications. Additionally, they are coupled with reduced adverse effects and boosted quality and life span of the patient. Phytochemicals also help to boost the immune response of host's cells against carcinogenesis explosion. Moreover, they support to decrease, bypass, or silence molecular mechanism underlying chemoresistance including signaling cascades, cell cycle effectors, drug transporters, and nuclear transcription factors. On the other hand, plenty of outcomes regarding phytochemicals and cancer therapy from in vitro, in vivo, and preclinical trials are being carried out every day showing success to some extent. Considering this, it had been predicted that numerous cancers could be prevented just by upholding proper lifestyle alterations, while interfaces of the phytochemicals as cancer medication may uncover some economic, safe, and nontoxic anticancer therapeutic in the future. Besides, further efforts are justifiable to appreciate potency, metabolism, stabilities, polymorphism, toxicities, drug–drug interactions, pharmacokinetics, and dynamics, along with the formulations, degradation, and dosages regimens of phytochemicals.

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