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Review Article

Underlying Anticancer Mechanisms and Synergistic Combinations of Phytochemicals with Cancer Chemotherapeutics: Potential Benefits and Risks

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Cancer therapies are associated with various challenges including the emergence of multidrug resistant tumors, toxicological issues, severe side effects, and economic burden. To counteract these effects, natural products as substitutes and adjuvant therapies have received considerable attention owing to their safety, efficacy, and economic aspects. Various preclinical and clinical studies revealed that natural products and their combinations with chemotherapeutics mediate their anticancer effects via modulation of various signaling pathways implicated in promoting apoptosis, inhibiting excessive cellular proliferation, and mobilizing the immune system. Several lead phytochemicals including curcumin, resveratrol, quercetin, and cannabinoids synergistically act with cancer chemotherapeutics reducing cell proliferation and inducing apoptosis and cell cycle arrest. However, clinical studies on the subject matter are limited and need further extensive studies. It has been observed that patients undergoing chemotherapy use alternative therapies to ameliorate the symptoms associated with the use of chemotherapeutic agents. Nevertheless, some of the patients inform their physicians regarding herbal medicine during chemotherapy while others do not, and even most of the patients do not know the composition of herbal medicine they consume during chemotherapy. Herbal interactions with chemotherapeutics are associated with both beneficial and harmful aspects, but the beneficial aspect overweighs the harmful ones in terms of controlling the symptoms associated with the chemotherapy. Nonetheless, a large number of herbal medicines have been demonstrated to have synergistic effect with chemotherapy and alleviate the side effects of chemotherapeutic agents. The concomitant use of the majority of herbal medicines with chemotherapy has been demonstrated to be beneficial in multiple malignant tumors like cancer of blood, lungs, kidneys, liver, skin, and gastrointestinal tract. However, herbal medicines which possess positive interaction and improve the quality of life of patients should be sorted out and integrated with the chemotherapy. There should be a quality control system for the appraisal of herbal medicine, and there should also be an appropriate system of patient-doctor communication to counsel the patients regarding the beneficial and deleterious effects of the herbal medicine in combination with chemotherapy.

1. Introduction

Cancer is regarded as the second leading cause of death around the globe [1, 2]. In spite of a keen focus on the management of cancer, the scenario seems to require more time for the control of cancer and its complications. To date, chemotherapy is the leading strategy in the management of cancer [3]. However, the patients diagnosed with various types of neoplasia and going through chemotherapy face several side effects, and thus many people rely on complementary and alternative medicine (CAM) [4]. CAM comprises some modalities like herbal medicine, homeopathic medicine, nutritional supplements, and anthroposophic medicine in advanced countries. The use percentage of CAM after the diagnosis of cancer has been found to be 26.5% in Europe. Similarly, 44% of the patients with chronic lymphocytic leukemia use CAM in Germany. Likewise, 68% of patients with lymphoma have also been recorded to use CAM in USA. Another survey records that 56% of the patients in India use CAM after diagnosis of leukemia. Even in Canada, the use of CAM is not mistrusted in their medical system, and about 46% of the CAM user patients inform their physicians [5]. The use of CAM has been shifted toward integrative medicine, which means that CAM users will no longer hide from their physicians the fact that they are using CAM during chemotherapy; instead, the physician may encourage the prescription of CAM drugs which have been derived from evidence based complementary medicine. The use of CAM is practiced throughout the world with candid evidence for improving the quality of life in various types of patients including cancer patients. However, there exist a wide variety of interactions between the CAM and the chemotherapeutic drugs [6]. A lot of metabolic systems inside the human body interact differently with different classes of drugs. The herbal medicines have been found to interact with the metabolic system in the liver responsible for the breakdown and activation of the drugs that may be cytochrome P450 system or phase-II metabolic system of the body. Interaction definitely exists due to the nature of chemotherapeutic drugs, some of which, for example, cyclophosphamide and ifosfamide, become active after their metabolism in the liver. Therefore, the interaction of herbal medicine with the chemotherapeutic drugs is a point of concern throughout the world [7, 8]. This review focuses on the use of CAM, especially herbal medicine, during chemotherapy and its useful and harmful aspects for cancer patients.

2. Anticancer Phytochemicals

Phytochemicals are the active constituents of plant origin grouped as flavonoids, alkaloids, glycosides, carotenoids, anthraquinones, nitrogenous derivatives glucosinolates, phenolics, and organosulfur compounds and have been used for the treatment and prevention of various diseases either alone or in combination with other drugs [9–14] (Table 1, Figures 1, 2(a), and 2(b)). Phytochemicals and their derivatives exhibit wide range of therapeutic actions like antioxidant [24–26], anti-inflammatory [27, 28], antidiabetic [29–32], analgesic [33–36], anticancer [37–42], neuroprotective [43, 44], and antimicrobial activities [45–47] and are significant source for the investigation and development of new drugs [48]. The anticancer potential of a large number of phytochemicals as potent anticancer agents has been identified [42, 49], which may be due to inducing apoptosis, modulation of cell signaling pathways, prevention of epigenetic changes, cell cycle arrest, and deoxyribonucleic acid (DNA) damage [9]. Several anticancer agents of plant origin are approved for clinical use and include vincristine, vinblastine, taxol, topotecan, irinotecan, camptothecin derivatives, and epipodophyllotoxins [50]. Previous studies revealed that curcumin obtained from the roots of *Curcuma longa* L. exhibited anticancer effects through induction of apoptosis, inhibition of proliferation, and cell cycle arrest of a number of cancer cell lines [51]. Some organosulfur components of *Allium sativum* L., such as S-allylcysteine, have retarded the growth of tumors (chemically induced) in several animal models [52]. Cyanidin glycosides, quercetin derivatives, and chlorogenic acids are the important phytochemicals of *Aronia melanocarpa* (Michx.) Elliott exhibiting anticancer activities [53].

Epigallocatechin-3-gallate (EGCG), rutin, and quercetin of *Camellia sinensis* (green tea) have been reported for their anticancer and antimicrobial activities [50, 54, 55]. Vinblastine and vincristine are the alkaloids isolated from *Catharanthus roseus* (L.) G.Don, used synergistically in combination with other anticancer drugs for the treatment of various types of cancers such as breast cancer, advanced testicular cancer, lung cancers, lymphomas, Kaposi's sarcoma, and leukemia [56]. Gymnemagenol is a phytoconstituent of *Gymnema sylvestre* (Retz.) R.Br. ex Sm. whose anticancer potential has been evaluated on HeLa cancer cell lines. MTT cell proliferation assay was used to determine the cytotoxic effect of gymnemagenol at various concentrations (5, 15, 25, and 50 μg/ml), and its cytotoxic effect on HeLa cells was found to be 73% with an IC_{50} value of 37 μg/ml [50]. The antitumor activity of *Scutellaria* genus flavonoids such as apigenin, baicalin, baicalein, scutellarein, chrysin, and wogonin has been reported showing positive interactions with various mechanisms of actions [57]. One study reported the antiproliferative effects of 7-hydroxy dihydro nuciferine obtained from *Nelumbo nucifera* Gaertn. on prostate, melanoma, and gastric cancer cells [58]. Baicalein isolated from *Oroxylum indicum* (L.) Kurz demonstrated antitumor effect on human cancer cell lines, and it was found to inhibit 50% of proliferation of HL-60 cell lines [59]. Apart from this, some other phytochemicals with anticancer potentials include 5-methoxyangenylalkannin, 6-gingerol, aloin, aloe emodin, artabotryside A, berberine, caffeic acid, capsaicin, crocetin, cucurbitacin glucosides E and I, cyanidin-3-glucoside, diosgenin, esculetin, ellagic acid, epicatechin, falcarindiol-3-acetate, falcarinol, ferulic acids, gallic acid, kaempferol, lupeol, lutein, protocatechuic acid, rhein, plumbagin, punicalagin, resveratrol, withaferin A, and xanthatin [9], Figures 2(a) and 2(b).

2.1. Mechanism of Anticancer Action of Phytochemicals. Phytochemicals confer their anticancer activities through a number of mechanisms including modulation of cell

Table 1: List of some important anticancer phytochemicals, their botanical sources, and underlying anticancer mechanisms.

Phytochemicals	Botanical source	Mode of action and study model	Mechanism of action	Ref.
Aloin, emodin	*Aloe vera* (L.) Burm.f.	Antiangiogenic activity, human lung cancer	Inducing apoptosis and decreasing autophagy	[15, 16]
Apigenin	*Petroselinum crispum* (Mill.) Fuss	Human breast cancer	Inducing apoptosis, modulating cell signaling pathways of cancer	[9, 17]
Curcumin	*Curcuma longa* L.	Stomach cancer, antiproliferative effect against human breast epithelial cancer cells	Reducing EMT; inducing apoptosis by blocking the PI3K/Akt pathway; downregulating MDM2, cyclin D1, and cyclin E; upregulating tumor suppressors p21, p27, and p53; inhibiting breast stem cells	[18, 19]
Epigallocatechin gallate (EGCG)	*Camellia sinensis* (L.) Kuntze	Anticancer activities	Inhibiting the functions of Hsp70 and Hsp90, inhibiting hypoxia and serum induced accumulation of HIF-1 alpha protein and VEGF expression	[19]
Resveratrol	*Polygonum cuspidatum*	Colon cancer, breast cancer, stomach cancer, ovary cancer, prostate cancer	Interfering with Akt activity and inducing apoptosis, causing G1 cell cycle arrest	[19]
Quercetin	*Vitis vinifera* L., *Citrullus colocynthis* (L.) Schrad., *Cupressus sempervirens* L.	Human breast cancer, Coca-2 cells, HepG2 cells	Arresting cell cycle and decreasing cell cycle genes, increasing caspase 3 and 9, modifying the toxic effect of H_2O_2,	[20, 21]
Ellagic acid	*Punica granatum* L.	Antiangiogenic activity	Antimutagenic activity, inhibiting DNA adduct formation, free radical scavenging activity, inhibiting VEGF and MMP pathway, decreasing the production of ATP in cancer cell	[9, 22]
Berberine	*Berberis lycium Royle*	Cervical cancer (SiHa) cells, human promyelocytic cells, HL-60 cells	Arresting cell cycle in S phase, decreasing VEGF in mice, decreasing MMP-2 and uPA, decreasing angiogenesis and metastasis	[9, 23]

signaling pathways, induction of apoptosis, prevention of epigenetic changes, cell cycle arrest, and DNA damage [9, 60]. Chemopreventive agents are also reported to exert their protecting effects by either preventing the formation of carcinogenic species or blocking the carcinogens interaction with biomolecules, thus inhibiting the formation of tumors [61] (Table 1 and Figure 3).

Cell signaling pathways such as mitogen-activated protein kinase (MAPK)/extracellular signal regulated kinases (ERK), nuclear factor kappa B (NF-Kb), and Janus-activated kinase (JAK)/signal transducer and activator of transcription proteins (STAT) are dysregulated or over-activated, altering the metabolism in different types of cancer cells leading to sustained angiogenesis, proliferation, dedifferentiation, and metastasis [9]. Modulation of these signaling pathways serves as a rational basis for the prevention and treatment of carcinogenesis by various drugs. The overactivity of MAPK/ERK signaling pathway as shown in tumors like melanoma was suppressed by various phytochemicals such as apigenin, crocetin, quercetin, and rhein [9]. The proliferation of human hepatoma HepG2 cells was inhibited by quercetin through inhibition of ERK and phosphatidylinositol-3-kinase (PI3K)/protein kinase B (Akt) pathways [21]. Gallic acid isolated from *Bergenia ciliata* (Haw.) Sternb. decreased the invasiveness of mouse brain endothelial cells and human glioblastoma U87 and U251 cells via downregulation of Ras/MAPK and PI3K/Akt signaling pathway [62]. The NF-kB signaling pathway plays a significant role in the progression of cancer stages such as proliferation, metastasis, and apoptosis. The phytochemicals which inhibit the NF-kB pathway include anethole, capsaicin, eugenol, sedanolide, genistein, gingerol, ursolic acid, and 3,3'-diindolylmethane [63].

Apoptosis is a process of programmed cell death which plays a significant role in eliminating tumor cells [64, 65]. Phytochemicals such as 5-methoxyangenylalkannin derived from *Alkanna tinctoria* (L.) Tausch and punicalagin obtained from *Punica granatum* L. have been reported to induce apoptosis by enhancing caspase 3 and 9 activities in human colorectal lymph nodal and small cell lung carcinomas, respectively [66]. In benzopyrene induced lung carcinogenesis mice model, esculetin of *Cichorium intybus* L. has induced apoptosis by improving oxidative stress and inhibiting Bcl-2 [67]. In human colon cancer, diosgenin from *Trigonella foenum*-graecum L. induced apoptosis cell (HT-29) by increasing caspase 3 activity and inhibiting B cell lymphoma 2 (Bcl-2) [68]. It has also been reported that artabotryside A induces apoptosis in glioma cells via arresting the cell cycle at G2/M phase in U87 [69] and caffeic acid induces apoptosis in hormone-sensitive breast cancer cell T47D by activating the Fas/FasL pathway and decreasing the aryl hydrocarbon receptor-induced CYP1A1 [70]. Apart

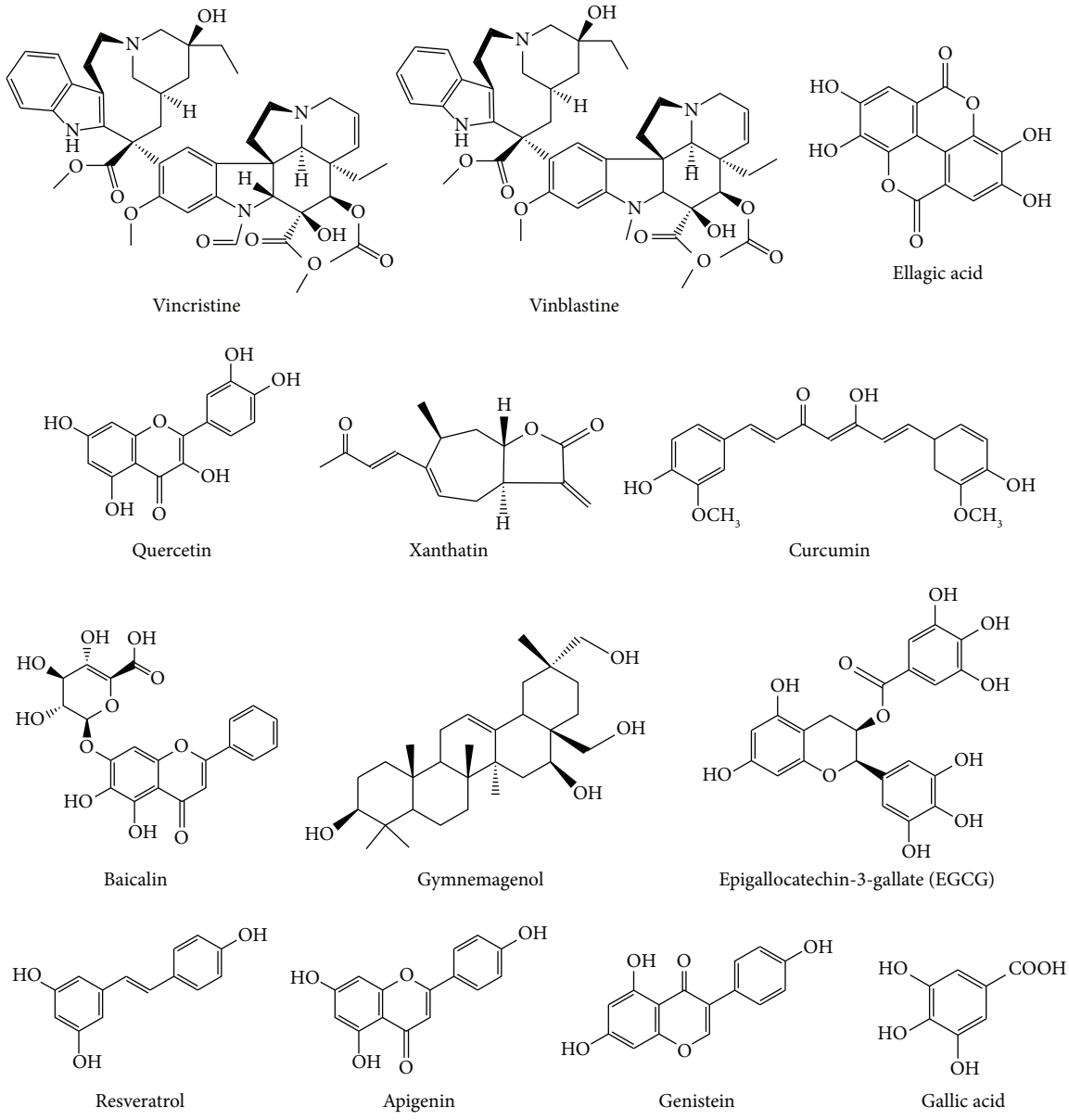
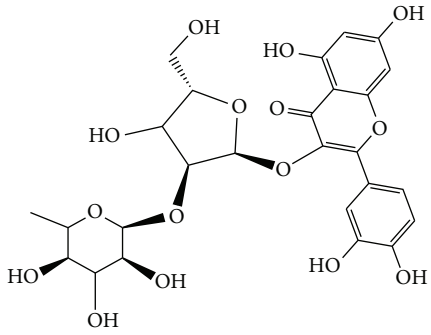


Figure 1: Structures of some lead anticancer phytochemicals.

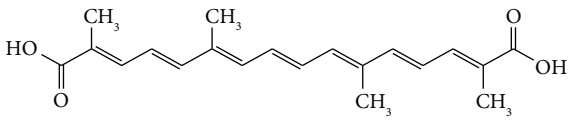
from this, other phytochemicals exhibiting anticancer effects through induction of apoptosis may include falcarindiol-3-acetate, lutein, rhein, apigenin, caffeic acid, capsaicin, kaempferol, and punicalagin [9].

The progression of cell cycle depends on the activation of cyclin dependent kinases (CDKs), and the arresting of cell cycle is controlled by cyclin dependent kinase inhibitors (CKIs), both of which need synchronous proteolysis [71]. A large number of phytochemicals such as alkaloids, flavonoids, phenolic acids, coumarins, and steroidal derivatives have demonstrated inhibitory potentials for the progression of cell cycle. Ferulic acid obtained from *Allium cepa* has been reported to increase the expression of genes involved in the assembly of centrosomes and to arrest the cell cycle at S phase, which results in its inhibitory effect on the proliferation of colon cancer Caco-2 cells [72]. The antiproliferative activity of withaferin A isolated from *Withania somnifera* L. has been shown to arrest the cell cycle at G2 and M phase by reducing CDK level in various cancer cell lines [73]. In addition, other phytochemicals that have the potential to arrest cancer cell cycle may include 5-methoxyangenylalkannin, berberine, capsaicin, esculetin, and kaempferol [9].

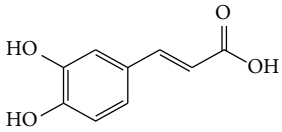
Epigenetic variations result in cancer due to chemical changes to histones and gene expression. Hyper- and hypomethylation of DNA lead to chromatin condensation and suppression of tumor inhibitory genes. In methylated cytosines, mutations cause improper expression of oncogenes [74]. It has been reported that sulforaphane inhibited hypermethylation in Nrf2 promoter through inhibition of DNA methyltransferase (DNMTs) and histone deacetylases (HDACs) in human bladder T24 cells and breast cells [75].



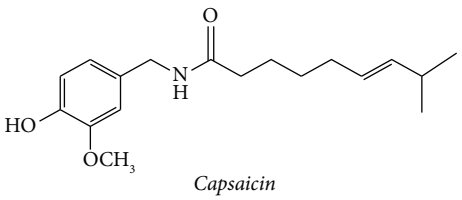
Artabotryside A



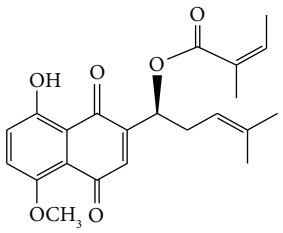
Crocetin



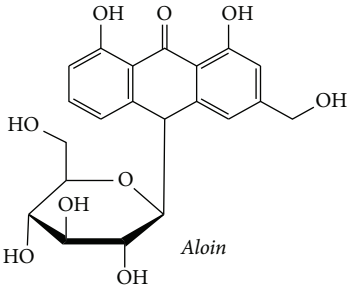
Caffeic acid



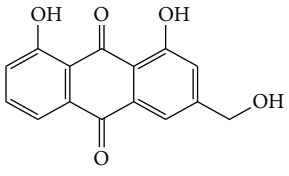
Capsaicin



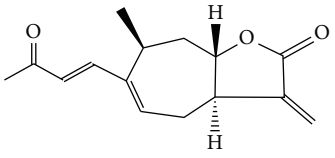
5-Methoxyangenylalkannin



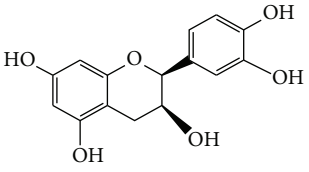
Aloin



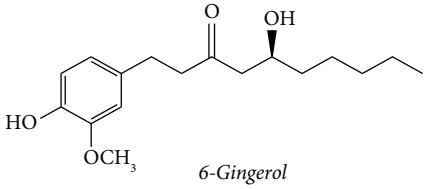
Aloe-emodin



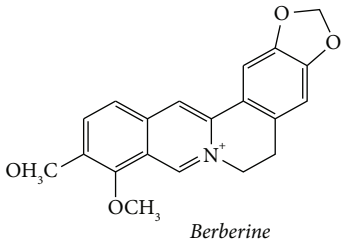
Xanthatin



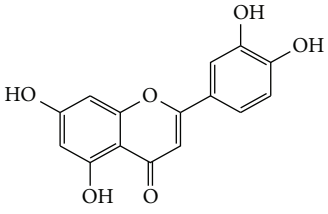
Epicatechin



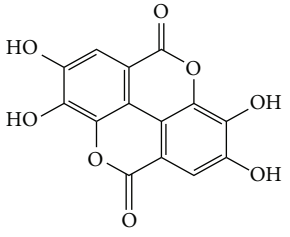
6-Gingerol



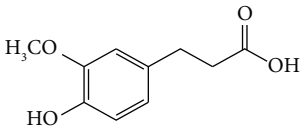
Berberine



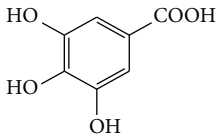
Luteolin



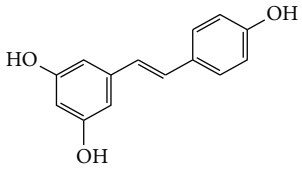
Ellagic acid



Ferulic acid



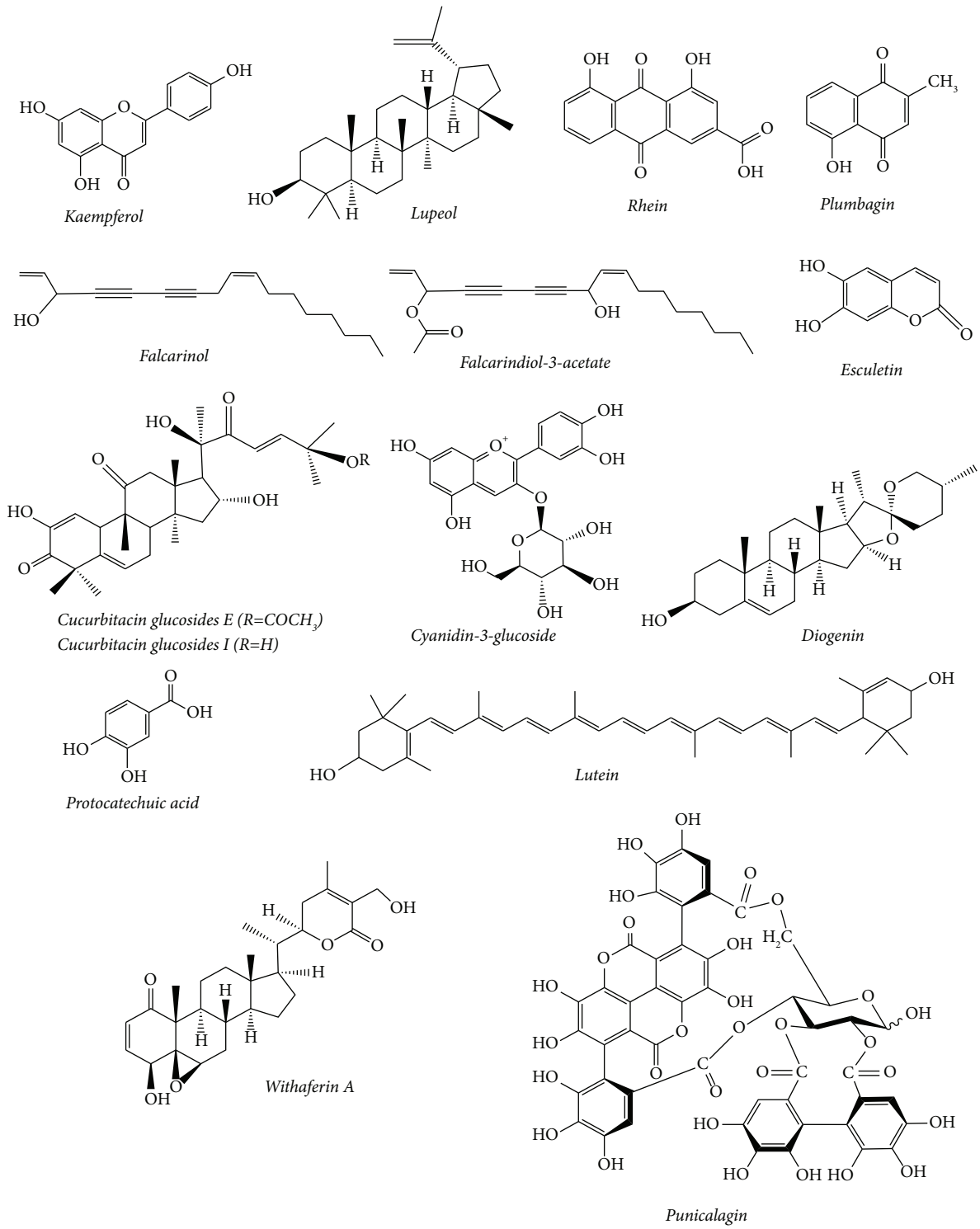
Gallic acid



Resveratrol

(a)

Figure 2: Continued.



(b)

Figure 2: Compounds having anticancer effects.

One study reported that genistein inhibited DNMTs, HDACs, and onco-miRNA while it upregulated the ataxia telangiectasia mutated (ATM) and phosphatase and tensin homolog (PTEN) in lung prostate and breast cancer cells to prevent their growth and invasion [76]. Mirza et al. reported that epigallocatechin-3-gallate prevented the progression of lung and breast cancers through inhibition of DNMT-1 and HDAC-1 and through demethylation of Wnt inhibitory factor-1 (WIF-1) promotor [77]. It was also found that due to demethylation of nuclear factor erythroid 2-related factor 2 (Nrf2) promoter, apigenin induced apoptosis and inhibited cell cycle as well as retarding HDACs

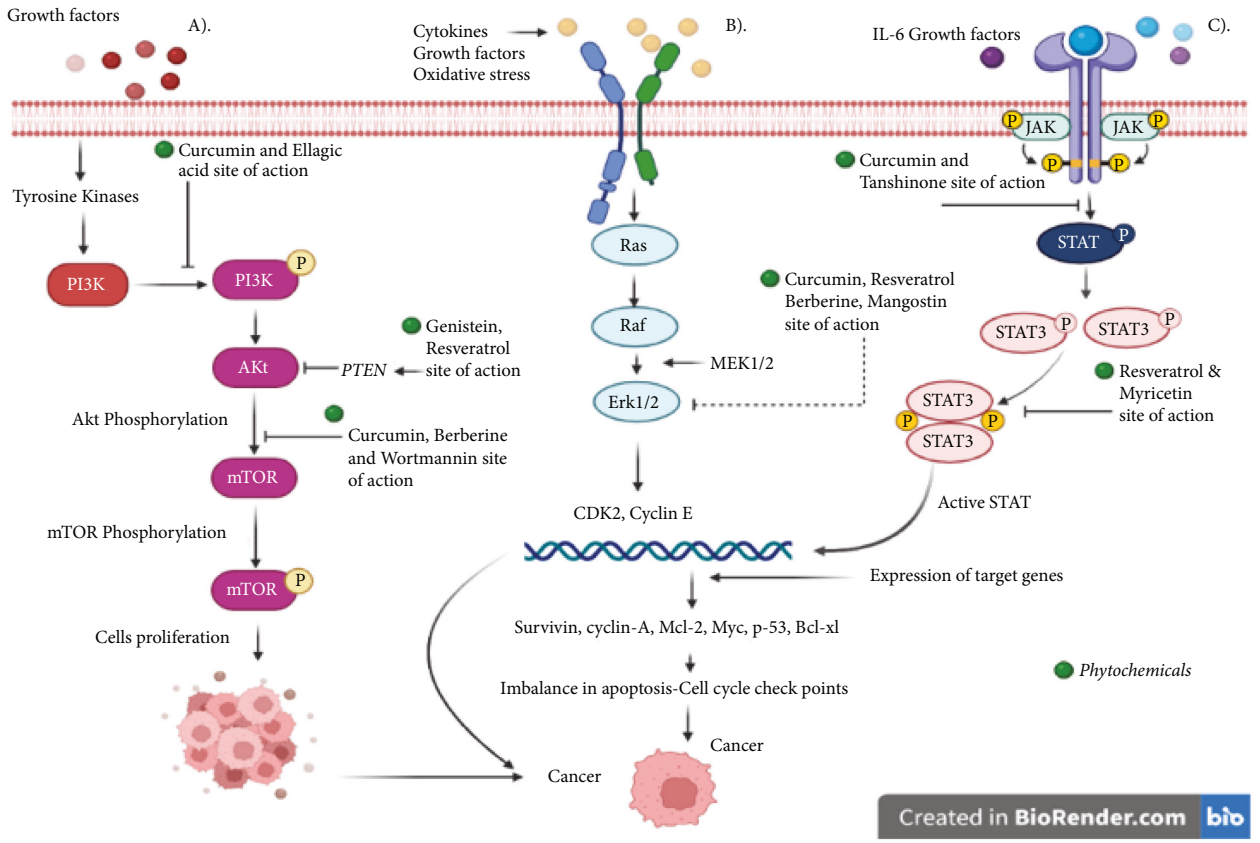


Figure 3: Mechanism underlying the anticancer potentials of some lead phytochemicals. (a) PI3K/Akt/mTOR pathway in cancer. (b) ERK1/2 pathway in cancer. (C) JAK/STAT pathway in cancer (created with https://BioRender.com).

and DNMTs in prostate cancer cells and malignant neuroblastoma [78].

The main causes of carcinogenesis involve DNA damage due to oxidative stress and mutation (mutagen induced DNA damage). In cells, the DNA repair mechanisms are activated when DNA is damaged. If the cell is unable to repair DNA damage, it will lead to apoptosis or cancer. Oncogenes are formed due to mutations in proto-oncogenes. The rate of carcinogenesis increased with the increasing exposure to several mutagens. To evaluate the antimutagenic and antigenotoxic activity of phytochemicals, various types of *in vitro* and *in vivo* tests have been devised [79]. Various phytochemicals have been reported to inhibit oxidant induced genotoxicity. Isoliquiritin apioside isolated from *Glycyrrhiza glabra* L. inhibited genotoxicity in human peripheral lymphocytes due to H_2O_2 induced DNA damage. In *Escherichia coli* PQ37, isoliquiritin apioside was further reported to reverse the mutations caused by 4-nitroquinoline-N-oxide (NQO) in Chromotest [80]. Chlorogenic acid and pelargonidin have been evaluated through *in vitro* comet assay to reduce the DNA damage and NQO related oxidative stress in human leukemia HL-60 cells [81]. Lycopene exhibited antimutagenic and anti-clastogenic activities through micronucleus assay against N-nitroso-N-methylurea (MNU) and aflatoxin B1 in the bone marrow of mice and was also found to prevent the frameshift and substitution mutations in *Salmonella typhimurium* TA-98 and *Salmonella typhimurium* TA-100, respectively [82]. One study revealed that melatonin, genistein, and caffeine inhibited the radiation induced mutations due to their antioxidant activities [83]. Apart from this, cyanidin, ferulic acid, ellagic acid, caffeic acid, and hydroxycinnamic acid are among the chemopreventive phytochemicals having antioxidant and antimutagenic activities [84].

3. Coadministration of Herbal Drugs with Chemotherapeutics against Various Cancers

The majority of phytochemicals tend to increase the therapeutic effect of other anticancer drugs either by increasing the bioavailability of the other drug, by blocking one or more targets of the signal transduction pathway, or by stabilizing the other drug in the system. The increased use of herbal drugs along with other conventional drugs may be due to high cost of treatment, increase in multidrug resistant strains, decrease in treatment efficacy, and most importantly complex multiple interconnected nodes of the cell signaling network where multiple modulating strategies play a significant role in effective treatment. Phytomedicines along with other conventional drugs exhibit beneficial effects through additive or synergistic actions of several chemical compounds acting at single or multiple target sites linked with a physiological process [85].

3.1. Effect of CAM on Gastric Cancer Therapy. An investigational study consisting of evaluation of prognosis of patients receiving chemotherapy along with Chinese herbal medicine (CHM) reveals that there was no rise in complications of incision after surgery and anastomosis. Moreover, the nutritional conditions of patients receiving CHM were significantly improved as compared to the control groups [86].

3.2. Natural Products in Kidney Cancer. Patients receiving chemotherapy may get various complications. One of the complications which is most commonly observed with cisplatinum is the nephrotoxicity. The effect of CHM has been recorded in patients receiving cisplatin. The CHM was in the form of decoction of Jian-Pi Yi-Qi Li-Shui. It was revealed that in patients receiving CHM, the cisplatin induced nephrotoxicity was prevented and the levels of creatinine, blood urea nitrogen, urea N-acetyl-beta-glucosaminidase, and beta-2-microglobulin were effectively decreased [87].

3.3. Natural Products in Hepatocarcinoma. The effect of CHM was evaluated in combination with the chemotherapy against hepatocarcinoma. The CHM consisted of Qingre Jiedu, Huoxue Huayu, and Fuzheng Guben while the chemotherapeutic agent consisted of cisplatin. A synergistic effect was observed by the integrative therapy. The hepatic cancer was found to be effectively recovered with the CHM in mice [88]. A similar study designed to evaluate the effect of CHM in combination with cisplatin chemotherapy was conducted in mice. As anticipated, there were significant inhibitions caused by combined chemotherapy as compared to the control groups. Therefore, the CHM (Bushen Huayu Jiedu recipe) has been found to be effective in combination with the chemotherapy for the management of tumors [89]. The improvement of patients receiving chemotherapy along with CHM has also been reported by a random study to decrease the liver toxicity in various cancer patients [90]. The chemotherapy in combination with the CHM not only reduces the chances of side effects associated with chemotherapy, but also shows a synergistic effect with the chemotherapeutic agents and exhibits a significant anticancer activity. One of the Chinese herbal medicines, i.e., Bushen Huayu Jiedu, has been reported for synergistic and antitumor activity in combination with the chemotherapy [89]. The effect of CHM in combination with chemotherapy on hepatocarcinoma has also been positively signified in randomized controlled trials. The study revealed that the CHM in combination with chemotherapeutic agents significantly benefits the patients and improves their quality of life [91]. One of the research teams has reported a case of liver toxicity caused by concomitant use of CHM along with the chemotherapeutic agent temozolomide against glioblastoma. The use of CHM along with the chemotherapeutic agents revealed that the liver toxicity may be caused by the CHM however, further detailed analysis of the study is required [92].

3.4. Effects of CAM on Gastrointestinal Cancer. A similar study has been conducted on patients having gastrointestinal cancer. The patients were receiving CHM, i.e., Fuzheng Yiliu, along with multiple chemotherapeutic drug combinations including i. etoposide + calcium leucovorin + 5-fluorouracil, ii. Cisplatin + calcium leucovorin + 5-fluorouracil (PLF), and iii. calcium leucovorin + 5-fluorouracil. The study concluded that the patients receiving the combined CHM and chemotherapeutic drugs exhibited significant therapeutic effect as compared to the control groups receiving only chemotherapeutic agents. Moreover, the toxic effects on GIT and bone marrow were minimized in the patients receiving the CHM [93]. The effect of CHM, i.e., Jian-Pi Yi-Qi, has also been studied in various patients having colorectal cancer and has been found to be effective in combination with the chemotherapeutic drugs [94]. Numerous chemotherapeutic drugs have been found to cause a variety of adverse effects. One of the pronounced effects on the gastrointestinal tract, which are common with most of the chemotherapeutic agents, is nausea and vomiting. For example, cisplatin has been found to cause oxidant gut injury, which is believed to be the main cause of nausea and vomiting in patients receiving this drug. Therefore, two antioxidant herbs, i.e., *Scutellaria baicalensis* and American ginseng berry, were used in combination with the cisplatin. The observations revealed that these antioxidant herbs were quite effective in prevention of cisplatin induced nausea and vomiting [95]. In another study, the effect of CHM along with chemotherapy was determined, and it was revealed that the chemotherapy induced nausea, vomiting, and fatigue have effectively been relieved [90]. A published report of patients having colorectal cancer has also revealed that the CHM in combination with chemotherapy greatly affects the treatment of colorectal cancer [96]. A recent report suggests that after gastric surgery, chemotherapy in combination with the CHM should be used positively because it greatly synergizes the activity of chemotherapy [86].

3.5. Effects of CAM on Phlebitis. The topical application of CHM has also been reported to possess an ameliorating effect. One of the toxic effect of chemotherapeutic drugs, i.e., phlebitis, has been investigated by a research team who figured out the effect of topical application of CHM along with oral chemotherapeutic drugs and revealed that CHM was effective in avoiding many toxic effects, specifically the phlebitis [97].

3.6. Effects on Lungs Cancer. The effect of a herbal product, i.e., javanica oil, was investigated against lung adenocarcinoma in combination with the chemotherapy. The chemotherapeutic agents employed were platinum and pemetrexed. The most common side effects occurring with these drugs are liver toxicity and leukopenia. The investigations revealed an enhanced chemotherapeutic response along with decreased chances of liver toxicity and leucopenia [98]. A similar study has been conducted in patients with lung cancer undergoing chemotherapy. The effect of CHM in combination with the chemotherapy was studied, and the

data revealed that there were decreased GIT toxicity, liver toxicity, and bone marrow toxicity in patients receiving combined regimen. This study was conducted on 235 patients [99]. Likewise, a randomized study has been carried out to find the effect of *Astragalus* based CHM along with chemotherapeutic agents. The effect was studied against non-small-cell lung cancer. The study revealed that the *Astragalus* based CHM in combination with the chemotherapeutic drugs improves cancer therapy. It was found to activate the natural killer cells and macrophages and similarly inhibit the T-helper cells cytokines. The study revealed increased survival of patients, improved performance, enhanced tumor response, and decreased toxicity [100].

3.7. Role of CAM in Relieving Cancer-Associated Pain. The effect of CHM in combination with chemotherapeutic agents has also been evaluated against cancer pain. The study was carried out in 4889 patients presenting with cancer pain. The observations revealed that the patients taking CHM along with chemotherapy exhibited significant decrease of cancer pain as compared to the patients using the chemotherapeutic agents alone [101].

3.8. Effects on Breast Cancer. A random study carried out on patients with breast cancer receiving chemotherapy along with CHM exhibited a vivid improvement in patients. It has been confirmed in this study that CHM improves the bone marrow and quality of life of patients with breast cancer [90].

4. Phytochemicals and Biological/ Physiological Systems

4.1. Phytochemicals and Immune System. The effect of various chemotherapeutic agents in combination with CHM comprised of immunomodulatory herbs, i.e., *Ganoderma lucidum*, *Codonopsis pilosula*, and *Angelicae sinensis*, was evaluated in different cancer patients, and it was revealed that CHM in combination with chemotherapeutic drugs enhances the immune system and ameliorates the potential to fight against cancer and to combat microbial infections [102]. A similar study also revealed that traditional Chinese medicine has been reported to improve the immune system during chemotherapy and have no hazardous effect or interaction with drugs used in the chemotherapy [103]. The improvement of the immune system has also been reported by a random study on patients receiving chemotherapy in combination with the CHM [90]. Immune system enhancement has also been reported by various researchers during chemotherapy along with CHM. Both the antibody mediated immunity and cell mediated immunity are enhanced by regulation of qi and blood and hence by harmonization and promotion of fluids in the body [104].

4.2. Effects of CAM on Cancer-Associated Nervous System Effects. The herbal medicine has been assessed in combination with the chemotherapy for the management of chemotherapy induced neuronal disorders. The overall study demonstrated that the chances of chemotherapy induced neuronal disorders, especially the chemotherapy induced peripheral neuropathy (CIPN), are significantly decreased or eliminated by the herbal medicine. Several natural compounds have been deemed responsible for decreasing the chances of CIPN; i.e., auraptenol can reverse the deleterious effect of vincristine, and so does cannabidiol for paclitaxel, curcumin for cisplatin or oxaliplatin, rutin and quercetin for oxaliplatin, verticinone for paclitaxel, and xylopic acid for vincristine [105].

4.3. Effect of CAM on Blood. Herbal medicine has been evaluated for the various hematologic toxicities caused by chemotherapy. The observations revealed that herbal medicine in combination with chemotherapeutic drugs minimizes the chances of blood toxicities and improves the quality of life of the patients undergoing chemotherapy [106]. Another pilot study conducted on adjuvant chemotherapy with herbal medicine figured out the safety of adjuvant chemotherapy. This study also revealed that the herbal medicine was completely tolerable by the patients [107].

4.4. CAM Effects on Chemotherapy Induced Fatigue. A thorough study has been conducted on hundred patients with breast cancer to evaluate the effect of CAM on chemotherapy induced fatigue. The investigation figured out that the chemotherapeutic agents used were Taxotere, adriamycin, cyclophosphamide, 5-fluorouracil, and epirubicin while the CAM used by the patients was *Withania somnifera*. Fatigue has previously been observed with the use of these chemotherapeutic agents but the use of CAM in combination with these chemotherapeutic agents revealed a significant elimination of fatigue and improved quality of life [108].

4.5. Effect on Cell Lines. Various cell lines are effective in vitro models in oncology research for discovery of drugs during preclinical research. They are an effective and useful source of cells representing specific types of cancers and are cost-effective as they do not need to induce tumors in living animals. Additionally, they retain specific genetic and other living cells characteristics during controlled conditions [109]. The effect of doxorubicin was studied against multidrug resistant cells, i.e., MCF-7 and A549. The effect has been studies in combination with CHM consisting of five herbs, i.e., *Curcuma wenyujin*, *Chrysanthemum indicum*, *Salvia chinensis*, *Ligusticum chuanxiong* Hort., and *Cassia tora* L. The investigations revealed a pronounced accumulation of doxorubicin inside the cancer cells and its significant antineoplastic effect [110].

5. Discussion

The induction of cancer requires a multitude of factors and so do its prevention and treatment. One of the multiple factors required for the cancer induction is the formation of

phlegm [111]. The phlegm is the point of focus in the recent reports due to its magnificent role in the cancer induction [112]. Keeping in mind the versatility of herbal medicine, some of the medicinal plants do have the potential for phlegm elimination from the body. Numerous reports have been published regarding the elimination of phlegm and regulation of qi in the blood [113]. In this article, we are focusing on the interaction of herbal medicine with the chemotherapeutic drugs or role of herbal medicine during chemotherapy. The main point of interaction between these two important categories is the liver, where the metabolism of chemotherapeutic drugs or natural products takes place [114]. The effectiveness of chemotherapy can be enhanced by concomitant use of certain herbal medicine which regulates the P450 system or phase-II metabolism. The herbal medicines have the same range of effects on the metabolism of the drugs as those of the grapefruits, alcohol, smoking, habits, and lifestyle [7]. The inhibition or activation of metabolizing enzymes in phase-I or phase-II confers a significant role in the carcinogenesis. For example, phase-I enzyme system activates some substances to become carcinogen, while the inhibition of this enzyme system avoids the formation of carcinogenic substances. Likewise, phase-II enzyme system also has a great role in cancer induction or prevention. Phase-II metabolism is mostly responsible for the elimination of a large number of foreign substances from the body including the carcinogens. A large number of herbal medicines have been reported to activate or inhibit the enzyme system responsible for metabolism or elimination of carcinogens. The natural compounds which inhibit the P450 system do not allow certain substances to become carcinogen and so avoid the chances of induction of cancer [115–117].

Similarly, natural compounds which activate phase-II metabolism do provide a chance for the carcinogens to bind with certain groups which eliminate them from the body via kidney. For example, the cabbage, cauliflower, Brussels sprouts, mustard green, and kale increase the activity of phase-II enzymes and are reported as anticarcinogenics [118]. Various chemotherapeutic drugs, i.e., cyclophosphamide, etoposide, teniposide, vincristine, vinblastine, vinorelbine, and vindesine, have been reported to interact with *Ginkgo biloba* and ginseng via the inhibition of CYP2C19 and CYP3A4. Likewise, garlic has interaction with dacarbazine via inhibition of CYP3A4; the anticancer antibiotics, alkylating agents, and platinum complex have interaction with *G. biloba* and grape seeds by scavenging of free radicals; and valerian has interaction with cyclophosphamide by CYP2C19 inhibition. Moreover, the kava kava has the potential to inhibit enzymes of the cytochrome P450 system [119]. Certain herbal medicine also activates the P450 enzyme system; for example, the *Hypericum* has been reported to be a potent inducer of CYP1A2, CYP2C9, CYP2B6, CYP3A4, and CYP2C19 [120].

A wide variety of plants have been reported to possess anticancer potentials [38, 121–123]. However, the use of herbal medicine in combination with the chemotherapy profoundly affects the efficacy of chemotherapeutic agents. The interaction may result in potential risk as well as benefiting the patients [124]. There may also be an interaction between chemotherapeutic agents and natural compounds if the patient is not using any herbal medicine, and the interaction may be due to the consumption of natural products in food, for example, spices, condiments, fruits juices, green and black teas, coffee, and vegetable oils [125–127]. However, the effect of interaction of medicinal plants and chemotherapeutic agents is significant. Therefore, in spite of the large number of beneficial interactions of herbal medicine with chemotherapeutic agents, there should be an appropriate appraisal system for the cancer patients going through chemotherapy. The appraisal system should include the integration of beneficial herbal products with the chemotherapeutic agents. The herbal products should be treated the same as the chemotherapeutic agents by the quality control and quality assurance section of the pharmaceuticals. As stated earlier, the combined therapy has profound effects on the cancer of kidney, lungs, gastrointestinal tract, breasts, blood, etc. Therefore, the positive interaction should be figured out precisely and incorporated into the chemotherapy as integrative chemotherapy.

6. Conclusion and Future Perspectives

Cancer being a highly complex disease is associated with numerous complications, and the conventional therapeutics have major side effects as well as economic burden on the patients. Subsequently, there is a dire need for the discovery of more useful anticancer phytochemicals and combination-agents which have less side effects and can potentially modify the therapeutic effects of anticancer drugs. About five thousand natural compounds, nutraceuticals, and extracts have been reported to have anticancer potentials. The current work was more focused on the combination of cancer chemotherapeutics with herbal agents and their synergistic or antagonistic effects when used concomitantly. Phytochemicals in combination with cancer therapeutics were found to mediate their positive anticancer effects via modulation of various signaling pathways which are implicated in promoting apoptosis, inhibiting cellular proliferation, and mobilizing the immune system. Phytochemicals and chemotherapeutics combinations mediate their inhibitory effects on cancer cells growth and are thus promising strategies for the discovery of more useful drugs. Based on the literature review of interaction of herbal medicine and chemotherapeutic agents, it may be concluded that the concomitant use of herbal medicine with anticancer drugs has synergistic, antagonistic, and deleterious effects. Therefore, the natural medicine producing synergistic effects should be sorted out and integrated into the chemotherapy for the very welfare of patients and human life. Patients should be informed about the beneficial as well as the harmful effects of herbal medicine, and proper counseling regarding the consumption of food containing natural products must be provided. Further detailed preclinical and epidemiological research is required for the identification and discovery of more useful synergistic anticancer phytochemicals. This will also help researchers to avoid antagonistic phytochemicals-chemotherapeutics combinations

and alternative medications to avoid failure of cancer therapy.

Abbreviations

CAM: Complementary and alternative medicine
EMT: Epithelial to mesenchymal transition
MDM2: Murine double minute 2
MMPs: Matrix metalloproteinases
VEGF: Vascular endothelial growth factor
MAPK: Mitogen-activated protein kinase
ERK: Extracellular signal regulated kinases
NF-Kb: Nuclear factor kappa B
JAK: Janus-activated kinase
STAT: Signal transducer and activator of transcription proteins
PI3K: Phosphatidylinositol-3-kinase
Akt: Protein kinase B
Bcl-2: B cell lymphoma 2
CDKs: Cyclin dependent kinases
CKIs: Cyclin dependent kinase inhibitors
DNMTs: DNA methyltransferase
HDACs: Histone deacetylases
ATM: Ataxia telangiectasia mutated
PTEN: Phosphatase and tensin homolog
WIF-1: Wnt inhibitory factor-1
Nrf2: Nuclear factor erythroid 2-related factor 2
NQO: 4-Nitroquinoline-N-oxide
MNU: N-nitroso-N-methylurea
CHM: Chinese herbal medicine.

Data Availability

The data used to support the findings of this study are available from the corresponding authors upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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