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Roles of Natural Compounds from Medicinal Plants in Cancer Treatment: Structure and Mode of Action at Molecular Level

Mahmood Rasool[1], Arif Malik[2], Abdul Manan[2], Mahwish Arooj[3], Mahmood Husain Qazi[3], Mohammad Amjad Kamal[4], Ishfaq Ahmed Sheikh[4], Siew Hua Gan[5], Muhammad Asif[6] and Muhammad Imran Naseer[1,*]

[1]*Center of Excellence in Genomic Medicine Research (CEGMR), King Abdulaziz University, Jeddah, Saudi Arabia;* [2]*Institute of Molecular Biology and Biotechnology, (IMBB), the University of Lahore, Lahore, Pakistan;* [3]*Center for Research in Molecular Medicine (CRiMM), the University of Lahore, Lahore, Pakistan;* [4]*King Fahd Medical Research Center (KFMRC), King Abdulaziz University, Jeddah, Saudi Arabia;* [5]*Human Genome Centre, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia;* [6]*Department of Biotechnology and Informatics, BUITEMS, Quetta, Pakistan*

M. Imran Naseer

Abstract: Every year, cancer takes the life of millions of people. Conventional treatments have produced unsatisfactory results for some types of cancer, and the side effects are extensive, leading to a shift in the focus of treatment towards alternative medicines. Indeed, medicinal plants have long been investigated by scientists for their anti-cancer properties. Some phytochemicals that are important active constituents of plants, including catechins, ursolic acid, silymarin, glycyrrhizin, ellagic acid, gallic acid and various types of flavonoids, have shown promise in future cancer management. The current review covers various aspects of cancer treatment based on medicinal plants at molecular level and sheds light on their structures and modes of action.

Keywords: Cancer treatment, phytochemicals, flavonoids, apoptosis.

INTRODUCTION

The prevalence of cancer in the world varies between Western and Eastern countries, with the former facing comparatively higher threats of prostate, colon, lung and breast cancers. There is a higher prevalence of neck, head and cervical cancer in North Asia (India), whereas stomach cancer is more commonly reported in Japan [1-3]. When the regulatory mechanism for the cell cycle is disturbed due to the dysregulation of the phosphorylation of proteins, cyclins and cyclin-dependent kinases (CDKs) responsible for cell division [4], the result could be catastrophic and lead to uncontrolled cell division or cancer. The current review elaborates multiple aspects of cancer treatment based on medicinal plants at the molecular level and their modes of action. The review has been divided into various sections, which includes following: multidrug resistance (MDR); MDR modulators for understanding of resistance in cancerous cells against the chemotherapeutic agents; tumorigenesis for the clarification of tumor spreading and multiple signaling pathways; phytochemical section to elaborate the anti-cancer natural compounds in various medicinal plants.

Even though chemotherapy and radiotherapy are widely employed for the treatment of various types of cancers, they are not without severe side effects [5]. Investigations and research on various medicinal plants have implicated that medicinal plants have promising roles in the treatment of various diseases, including cancer, as opposed to the modern and/or rationalized allopathic approaches to treatment [6].

In fact, various drugs currently used in cancer treatments are based on medicinal plants, namely vinblastine, topotecan, Taxol/paclitaxel, vincristine, etoposide and teniposide [7]. The continued existence of plant remedies for various disorders indicates their effectiveness, which is further enhanced by their comparatively better side effect profiles. Anti-cancer drugs from medicinal plants have the ability to boost the immune system and re-establish the body's homeostasis. The antioxidant properties of various medicinal plants further increase their value. Many of the current plant-based drugs have the ability to induce apoptosis in multiple cancerous cells of human origin [6]. However, there is a continuous need for investigation in the field of medicinal plants for the management of cancer, especially with regard to the synthesis of anti-cancer drugs, chemotherapeutic strategies and drug combinations.

Anti-cancer agents from natural compounds need to be explored not only at physiological and cellular levels but also at the molecular level. For example, Taxol is a potent natural agent that continues to be used in the treatment of refractory ovarian and breast cancers [8]. Alfalfa, considered to be a nutritious food product, has anti-fungal and anti-bacterial activities and enhances the generation of white

*Address correspondence to this author at the Center of Excellence in Genomic Medicine Research (CEGMR), Post Box No. 80216, King Abdulaziz University, Jeddah, 21589 Saudi Arabia; Tel: +966-6401000 ext 25211; Fax: +966-6952521; E-mail: mimrannaseer@yahoo.com

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Table 1. Various plants used in different types of cell lines with regard to reversing multidrug resistance (MDR).

Plant/Compound	Protein/Cell Lines	Reversal of MDR	Cancer Type	References
Stemona curtisii	KB-VI cells	Vinblastine, paclitaxel, colchicines	Cervical carcinoma with ↑ P-gp expression	[20]
Alisma orientalis	HepG2-DR, K562-DR	Actinomycin D, puromycin, paclitaxel, vinblastine, doxorubicin	-	[21]
Lignans	HL60/Adriamycin MDR model	MDR associated protein-1	-	[22]
Flavonoids	Breast cancer resistance protein (BCRP)	An ATP-binding cassette (ABC) transporter	Breast cancer	[23]
Epigallocatechin gallate (EGCG), green tea polyphenol	KB-A1 cells	Modulation of P-gp	-	[24]
Lobelia inflata	Resistant cells	↓ P-gp activity, doxorubicin	-	[25]
Curcumin (turmeric)	L1210/ADR cells	↓ *mdr1b gene* (↓ P-gp)	-	[26]
Paris polyphylla (polyphyllin D)	R-HepG2 cells	Elicit apoptosis in cancerous cells, Mitochondrial damage	-	[27, 28]
Magnolia grandiflora (Honokiol)	MCF-7/ADR cells	↓ angiogenesis, ↓ P-gp, ↑ apoptosis	Breast cancer	[29]
Biochanin A, Daidzein, Fisetin, Morin, Naringenin, Quercetin, Silymarin (Flavonoids)	MCF-7/ADR cells	Daunomycin (DNM)	Breast cancer	[30]

↓ decrease, ↑ increase

blood cells [6] in addition to having the ability to counteract the harmful effects of chemotherapy. Similarly, *Andrographis paniculata* has been found to be effective against various cancers and viral and bacterial infections, particularly human immunodeficiency virus [9, 10]. This plant has a dramatic effect in maturing cancerous cells such that cancerous cells cease their uncontrolled growth. It has also been reported to reduce the possibility of gastric, breast and prostate cancers [9, 11, 12]. Another important anti-cancer plant is rosemary, which has anti-oxidative, anti-septic and anti-spasmodic features. Rosemary assists in preventing cancer by preventing carcinogenic substances from attaching to cells, which would cause mutations that lead to cancer [13].

CANCEROUS CELLS AND MULTIDRUG RESISTANCE (MDR)

Many cancer cells show resistance toward chemotherapeutic agents, resulting in the failure of anti-cancer drugs, a biological phenomenon referred to as multidrug resistance (MDR). P-glycoprotein (P-gp, transport molecule; 170 kD) has been found to be associated with drug resistance in ovarian cell line studies [14]. Cancerous cell resistance toward chemotherapeutic drugs is due to two main reasons: i) the absorption, distribution, metabolism and elimination of a drug, which depends on the need of the biological system and is controlled by the genetic makeup of the organism, potentially producing various cellular responses that do not allow the drug to reach threshold levels to exert its pharmacological mechanism and ii) the origin of cancerous cells in terms of tissue and vasculature functionality, whereby drug is unable to reach the tumor site to perform its action properly, thus leading to chemotherapy resistance [15].

Moreover, enzyme-based resistance, which is called non-transport/non-classical resistance, involving glutathione-S-transferase (GST) is associated with xenobiotic metabolism and is responsible for the biotransformation of many chemotherapeutic drugs (organic molecules) in cell metabolism. The elevated levels of GST metabolize the drug to its end products, with reduced drug action and a high rate of elimination [16-18].

MDR INHIBITORS/MODULATORS

Compounds involved in reversing the resistance against anti-cancer drugs are either referred to as chemo-sensitizers, MDR modulators on inhibitors [19]. Inhibitors belong to various chemical groups and have been divided as 1st, 2nd and 3rd generations of MDR reversal agents, depending on their relative toxicity toward non-cancerous cells and their affinity for P-gp [15]. Medicinal plant extracts show a significant reversal of resistance towards chemotherapeutic agents including vinblastine against cervical carcinoma [20]. Another example is EGCG that is responsible for modulating the P-gp in human cancer cells and increases the accumulation of chemotherapeutic agent doxorubicin in cancerous cells [24]. Recent investigations have shown that natural phytochemicals are good and potential MDR inhibitors /modulators (Table **1**).

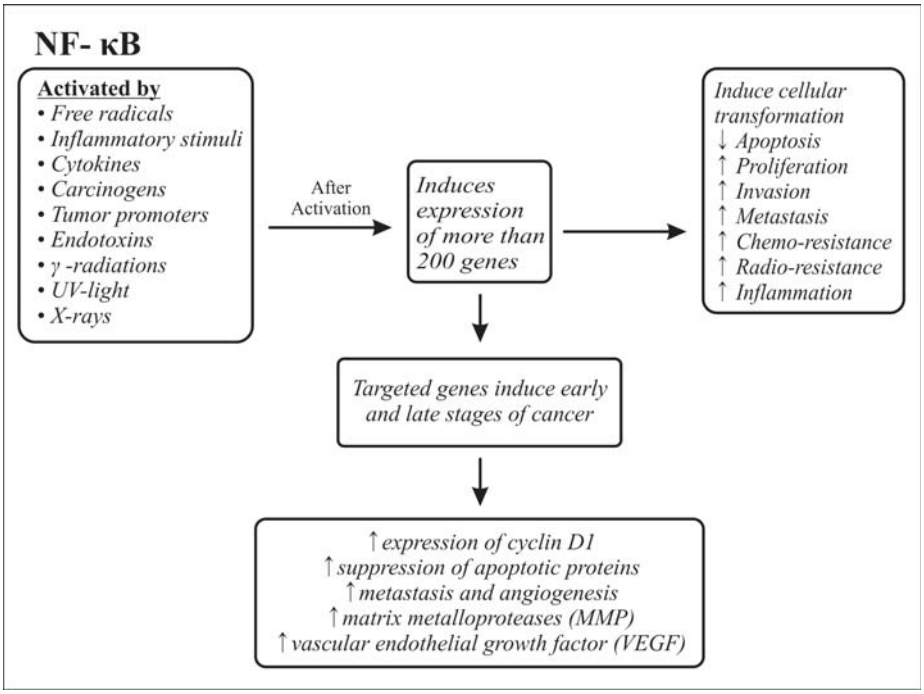

Fig. (1). Role of NF-κB in normal and cancerous cells.

TUMORIGENESIS

Various environmental factors referred to as carcinogens, including industrial emissions, smoke, heavy metals and gasoline vapors, are responsible for the activation of oncogenes, producing tumors in specific tissues. Another important biological process that accompanies tumor progression is angiogenesis or the development of new blood vessels. Cancerous tissue needs to be constantly supplied with oxygen and nutrients to support its rapid growth. Tumor cells generate signaling molecules in the extracellular environment that encounter normal host cells to activate genes in the host cells to synthesize proteins that guide the cells to produce new blood vessels. Various signaling molecules (angiogenic factors) are released by tumor cells. Many phytochemicals that have chemopreventive properties have been associated with these angiogenic targets, including curcumin, catechins, luteolin, genistein and resveratrol [31-38].

The management of a biological system in a continuous, normal steady state and the shift toward a cancerous state are complex, multistep processes. Various types of factors, both intracellular and extracellular, are involved at the molecular level [39]. Food components and drugs used for cancer treatment share many common targets. The drugs used for the treatment of cancer utilize multiple targets depending upon the type of cancer. The overall environment of a biological system is accompanied by multiple cell survival and death signaling pathways [39] including growth factor pathways, apoptotic and antiapoptotic proteins, protein kinases, cell cycle proteins, transcriptional factors and most importantly those pathways and proteins involved in metastasis [39].

Normally, there is a mechanism for the termination of signaling through the PI3K-PKB pathway. PIP3-specific phosphatase (the PTEN gene in humans) removes the phosphate group from position 3 of PIP3 (phosphatidylinositol 3, 4, 5-triphosphate) to produce PIP2 (phosphatidylinositol 4, 5-bisphosphate), abolishing the binding site for PKB, thereby blocking the signaling cascade [40]. In various cancerous cells, a defect has been found in the PTEN gene [41]. In addition to this, an abnormally high level of PIP3 and PKB activity are also observed in different cancerous cell lines. Hence, there is a continuous signal for cell division that leads to growth of the tumor [40].

In the case of breast cancer, tamoxifen, which is an antagonist of estrogen, is administered to treat cancer cells that interact with steroid receptors [42]. The proliferation of cancerous cells in a few types of breast cancer depends on the continuous presence of estrogen hormone. Tamoxifen competes with the hormone for binding to the estrogen receptor, with the drug-receptor complex having almost no or little effect on gene expression. As a result, the administration of tamoxifen helps in slowing down or halting the growth of remaining cancerous cells in breast cancer during hormone-dependent chemotherapy [42] but some side effects of tamoxifen have also been reported. Medicinal plants are not only useful in cancer treatment but can also alleviate the side effects produced by various chemo- and radiotherapies.

MODE OF ACTION OF PHYTOCHEMICALS INVOLVED IN CANCER PREVENTION

The phytochemicals present in plants act in multiple ways when applied *in vitro* and/or *in vivo* and exhibit various forms of action, including anti-cancer activity. In normal cells, various cell signaling pathways, such as the MAPK [44] signaling pathway, NF-κB [44, 84] and AP-1 pathways [44] (Figs. **1** and **2**), c-Jun activity suppression, β-catenin or Wnt pathway and growth factor receptor-mediated signaling pathways, are essentially involved in the survival and main-

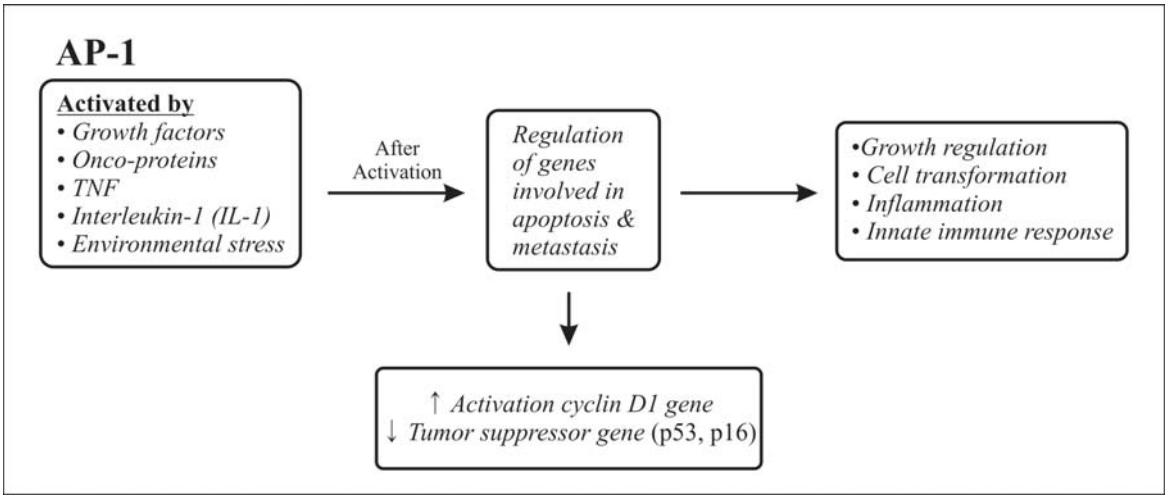

Fig. (2). Role of AP-1 in normal and cancerous cells.

tenance of the internal environment of cells [37]. The cell cycle is necessary in organisms, while apoptosis is also a necessary evil. Free radicals and reactive oxygen species (ROS) are produced and scavenged by anti-oxidants in the cell to minimize cellular damage in the natural environment of a biological system. Moreover, the expression of oncogenes is halted, and the cell can perform its normal physiological functions.

In the case of cancerous cells, all the normal process are interrupted, and the cells divide at an exponential rate and exhibit unique features, as opposed to normal cells. Phytochemicals such as gallic acid, ellagic acid, caffeic acid, lignans, catechin, quercetin and curcuminoids have anti-oxidant as well as anti-aging activities [38, 43-47]. These compounds can therefore scavenge the free radicals and ROS present in cells, such as singlet oxygen, hydroxyl radical, nitric oxide, peroxyl radical and superoxide anion, increasing the activity of superoxide dismutase (SOD) while decreasing the rate of lipid peroxidation (LPO). Phenolic acids and various types of flavonoids, such as daidzein, quercetin, hesperetin, apigenin, luteolin, silymarin, genistein, epigallocatechin gallate (EGCG) and kaempferol, as well as resveratrol, curcumin, lignins and quinines [43, 45, 48-51] help to inhibit cell proliferation, oncogene expression and vascular endothelial growth factor (VEGF). They can also induce the phenomenon in which tumor suppressor gene expression occurs along with preventing the binding of carcinogens to DNA.

Cinnamic acids, paradol, gingerol, rosmarinic acid, curcumin, sesamol (lignan), coumarin, tannic acid and flavonoids including silymarin, genistein, quercetin and luteolin [37, 43-45, 52-56] suppress the synthesis of tumor necrosis factor (TNF) [84], inducible nitric oxide synthase (iNOS), lipo-oxygenase (LOX), chemokines, pro-inflammatory cytokines growth factors related to tumors and various inflammatory molecules in the cytoplasm. Chlorogenic acid, ellagic acid, caffeic acid, resveratrol, curcumin, quinines, flavonoids (EGCG, apigenin, quercetin) and podophyllotoxin [43, 45, 57-63] can help in the inhibition of various enzymes that in turn are responsible for blocking the activation of carcinogen-like signal transduction enzymes, cyclooxygenase-2 (COX-2) [44], urease, telomerase, iNOS, topoisomerases I and II and DNA methyltransferases, leading to the reactivation of tumor suppressor genes (*p16*).

Flavonoids have been found to minimize the risk of many disorders, particularly cancer, and are associated with diverse bioactivities due to their natural ability to scavenge free radicals and ROS as powerful anti-oxidants [64]. Flavonoids arrest the cell cycle in cancerous cells by inducing apoptosis and inhibiting MDR proteins, angiogenesis, proliferation and carcinogenic metabolic activation processes and promoting differentiation [64-67]. Silymarin, genistein, green tea (EGCG), quercetin, luteolin and apigenin have demonstrated anti-angiogenesis and anti-mutagenic behaviors [68]. Moreover, apigenin halts the expression of adhesion molecules such as vascular cell adhesion molecule-1**,** intercellular adhesion molecule 1 (VCAM-1, ICAM-1) and E-selectin, inhibits the synthesis of prostaglandin and interleukins-6 and -8 (IL-6 and -8) and induces cell differentiation and the expression of the interferon-γ gene [69, 70]. A study indicated that Andrographolide is responsible in increasing the expression of caspase-3, bax and p53 (Fig. **3**) in a human breast cancer cell line [78]. It is also responsible for the decreased expression of E-selectin and IL-6 [80, 81]. Various medicinal plants are indicated with their use in various cancer types in Table **2**.

CONCLUSION

Recently, there has been a shift from synthetic to natural compounds in the management of cancer. The revival of plant-based remedies is due to the effectiveness and fewer side effects when compared to modern drugs. To date, many compounds, such as catechins, ursolic acid, silymarin, glycyrrhizin, ellagic acid, gallic acid and various types of flavonoids, have been investigated for their anticancer activities at the molecular level, and some have shown promising results. Nevertheless, there is a broad range of unexplored natural compounds that could be better anticancer candidates. Accordingly, there is a strong need for focus on various medicinal plants and their active constituents in cancer research. Using *in silico* studies, the structures of these natural compounds can be further modified according to the target site, which can result in improved results because most

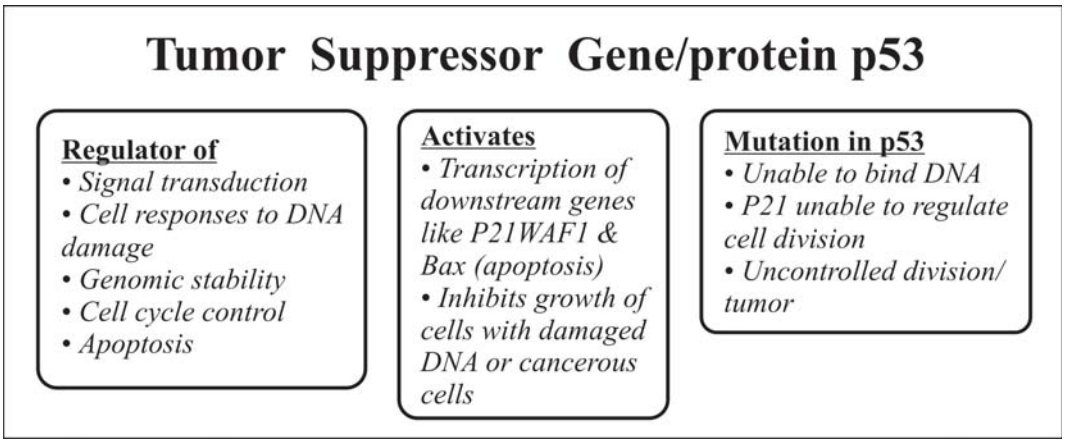

Fig. (3). Role of tumor suppressor gene/protein p53 in normal and cancerous cells.

Table 2. Various medicinal plants used in cancer study and/or management.

Plant	Active Compounds	Types of Cancer	References
Aegle marmelos	Lupeol	Breast	[71]
Aloe vera	Acemannan, emodin, lectins, alexin B	Stomach, neuro-ectodermal tumor, leukemia, liver, breast	[72]
Alpinia galangal	Acetoxy-chavicol-acetate (ACA)	Melanoma, breast, lung, stomach, colon, prostate	[73-75]
Amoora rohituka	Amooranin	Breast, pancrease, colon, leukemia	[76, 77]
Andrographis paniculata	Andrographolide	Breast, ovary, gastric, prostate, bone metastasis, leukemia	[78-83]
Azadirachta indica	Nimbolide, azadirachtin, liminoids	Leukemia, breast, stomach, prostate, skin, colon	[84-88]
Bauhinia variegata	Glycoside of cyanidin, malvidin, peonidin and kaempferol galactoside	Breast, lung, liver, oral cavity, larynx, malignant ascites	[89, 90]
Berberis libanotica, *B. vulgaris*	Berberine, bermamine, chelidonic acid, columbamine, hydrastine, isotetrandrine, jacaranone, magnoflorine, oxycanthine, palmatine, citric acid	Prostate, breast, liver, colon, leukemia, intracranial tumor, stomach, cavity cancer	[91-93]
Betula alba	Betulinic acid	Prostate	[94]
Camptotheca acuminata	Camptothecin, topotecan, CPT-11, 9-aminocamptothecin	Prevents cancer-promoting cell mutations	[95]
Catharanthus roseus	Vinblastine, Vincristine, Vindesine, Vinorelbine	Breast, leukemia	[96, 97]
Curcuma longa	Curcumin, curcuminoids	Breast, leukemia, colon, CNS, melanoma	[98]
Emblica officinalis	Ellagic acid, gallic acid, quercetin, kaempferol, emblicanin, flavonoids, glycosides, proanthocyanidins	Ovarian, breast, skin, stomach, liver, malignant ascites	[99-101]
Ginkgo biloba	Ginkgetin, ginkoglides-A,B	Breast, ovary, colon, prostate	[102-105]
Glycine max	Genistein, daidzein, saponins	Breast, skin, cervix, lung, liver, kidney	[106-108]
Glycyrrhiza glabra	Glycyrrhizin, flavonoids	Prostate, breast, colon, leukemia, liver, skin	[109-113]
Morinda citrifolia	Damnacanthol, NB10, NB11	Breast, lung, pancreas, leukemia, colon	[114-117]
Nigella sativa	Thymoquinone, dithymoquinone	Breast, prostate, colon, pancreas, leukemia	[118-122]
Nothapodytes foetida	Acetylcamptothecin, Camptothecin, Scopolectin	Prevents cancer-promoting cell mutations, inhibitor of DNA topoisomerase	[123]

Table 2. contd….

Plant	Active Compounds	Types of Cancer	References
Ocimum sanctum	Eugenol, orientin, vicenin, ursolic acid, linolenic acid, rosmarinic acid	Breast, liver	[124, 125]
Oldenlandia diffusa	Oldenlandosides, stigmasterol, ursolic acid, oleanolic acid	Lung, ovary, prostate, liver, breast, colon, leukemia	[126-129]
Panax ginseng	Ginsenosides-panaxadiol, panaxatriol, compound K	Ovary, lung, colon, leukemia	[130-133]
Plumbago zeylanica	Plumbagin	Breast, liver, prostate, leukemia	[134-136]
Podophyllum hexandrum	Podophyllotoxin, podophyllin	Breast, liver, lung, prostate, colon, neuroblastoma, CNS	[137, 138]
Prunella vulgaris	Oleanolic acid, ursolic acid	Breast, uterine, cervix, liver, colon, lung, stomach, leukemia	[139-141]
Psoralea corylifolia	Corylfolinin, bavachinin, psoralen	Breast, leukemia	[142, 143]
Rhodiola rosea	Rhodioloside, P-tyrosol	Breast	[144]
Rubia cordifolia	Mollugin, rubiadin, rubidianin	Colon, kidney, liver, oral, ovary	[145-148]
Saussurea lappa	Cynaropicrin, costunolide dehydrocostuslactone, makkolactone, shikokiols	Neuroblastoma, breast, liver, prostate, leukemia	[149-153]
Semecarpus anacardium	Biflavonoids, bhilavinol	Liver, leukemia	[154, 155]
Solanum nigrum	Solamargine, solasonine, lunasin	Breast, liver, colon	[156-158]
Trigonella foenum	Galactomannan, folic acid, flavonoids	Breast	[159]
Viscum album	Viscumin, viscotoxin, digallic acid	Breast	[160]
Withania somnifera	Withaferin A, sitoindoside IX, physagulin D, withanoside IV, viscosalactone B	Breast, lung, colon, cervix, prostate, sarcoma-180	[161-166]
Zingiber officinale	Gingerols, 6-shogaol	Breast, liver, ovary	[167-170]

studies have been conducted using cell models. To validate these results, there is also an urgent need for the expansion of these studies in animal models.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interests.

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