

A Review of Plants with Anticancer Properties

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Abstract

Traditional herbal treatments are becoming increasingly popular owing to their ease of use, low cost, and absence of side effects. Several naturally occurring plant-based substances, including curcumin, resveratrol, and quercetin, have shown promise as anticancer treatments. Recent studies have concentrated on discovering drug-like molecules generated from these plants that are less harmful to healthy cells while specifically targeting sick cells. Unlike traditional pharmaceuticals, these molecules have structures that are similar to those found in nature. Antioxidant, anti-inflammatory, antimutagenic, and apoptosis-inducing qualities found in herbal substances aid in the early detection of cancer. Adequate dietary consumption of these products may contribute to the prevention and treatment of cancers by inducing cell cycle arrest, apoptosis, regulating carcinogen metabolism and oncogenic expression, inhibiting cell adhesion, proliferation, and migration, and blocking signaling pathways critical for cancer progression. Herbal remedies are a novel and secure way to cancer therapy that provides both efficacy and safety. The purpose of this review is to shed light on some of these plants and their confirmed anticancer activities.

Keywords: Cancer therapy; Herbs; Plants; Anticancer; Cytotoxic.

Introduction

Ethnomedicine and herbal compounds used for cancer treatment

There has been a significant global emphasis in recent years on performing plant research

with the goal of identifying drug-like molecules derived from traditional medicinal plants [1]. Several naturally occurring plant-based compounds, including curcumin, resveratrol, and quercetin, have shown great promise as adjuvant chemotherapy medicines and are gaining recognition for their

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anticancer properties. Furthermore, these naturally occurring chemicals frequently have lower toxicity toward healthy cells and, in certain situations, a propensity for targeting aberrant or sick cells [1]. As a result, many of the medications on the market today have structures that are similar to natural compounds. The herbal components have a variety of qualities, including antioxidant, anti-inflammatory, antimutagenic, and apoptosis-inducing activities, which aid in the

early diagnosis of cancer (Figure 1). By causing cell cycle arrest, apoptosis, regulating carcinogen metabolism and oncogenic expression, inhibiting cell adhesion, proliferation, and migration, and blocking signaling pathways crucial for cancer progression, adequate dietary consumption of these herbal products may help with the prevention and treatment of breast cancer. [2].

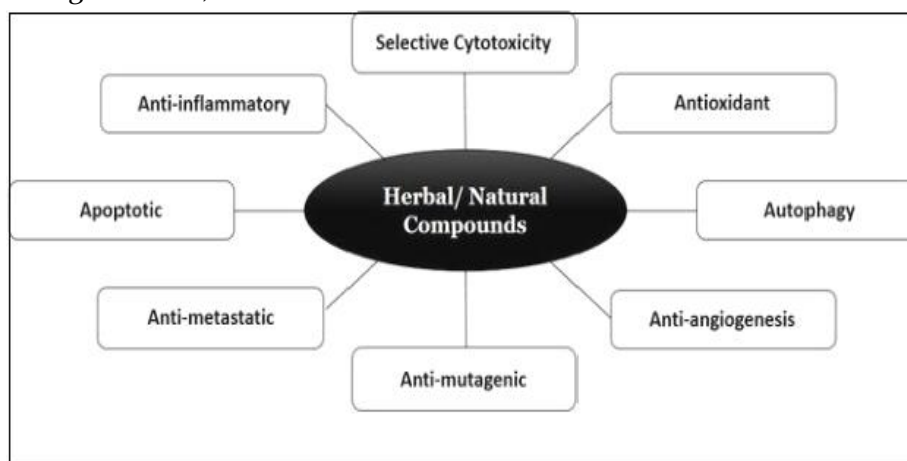


Figure 1: Features of herbal compounds that attribute to their anticancer activity [3].

Plants used globally for cancer control/management

Plants create a plethora of chemical compounds that do not play a direct role in their growth. These chemicals, known as secondary metabolites, include tannins, alkaloids, terpenoids, flavonoids, pigments, and pigment-like molecules. Secondary metabolites have been shown to have biological effects on hematopoietic cells [4], lipids [5], and cardiovascular systems [6], as well as anti-inflammatory, anticancer, and contraceptive effects.

The improvement of cancer treatment has been greatly aided by the identification of

secondary compounds in natural goods and therapeutic herbs. Plants inhibit cancer-promoting enzymes, speed up DNA repair, encourage the synthesis of antitumor enzymes in cells, boost immunity, and provide antioxidant effects to combat cancer [7]. Finding plants with cytotoxic properties that can replace chemotherapy and other time-consuming cancer treatments is essential [8].

Achillea wilhelmsii (yarrow)

When tested on colon cancer cells (HT-29), it was shown in research by Dalali Isfahani, et al., [9] that the essential oil made from the leaves of the *Achillea wilhelmsii* plant had

more potent cytotoxic effects than the methanol extracts. The effectiveness of methanol extracts from the plant's leaves against breast, stomach, and colon cancer cell lines has also been shown in other research investigations [10].

Flavonoids in particular, which cause apoptosis and hence prevent the growth of cancer cells, are present in the plant's methanol extract [11]. Furthermore, Dokhani et al., found that the monoterpenes 1,8-cineole and -pinene, which are present in sizable amounts in the essential oil extracted from the plant's leaves, cause human melanoma cells to undergo apoptosis.

Ageratum conyzoides (billygoat weed plant)

Using human lung cancer (A549) and mouse leukemia (P388) cell lines as test subjects, Adebayo, et al., [12] examined the cytotoxic effects of the ethyl acetate extract from *Ageratum conyzoides*.

Both cell lines exposed to the extract showed cytotoxicity. Additionally, it was discovered that the leaf extract of *A. conyzoides* prevented the growth of a number of cancer cell lines, including SF-767, LNCaP, PC-3, and SF-763 [13]. According to Adebayo, et al., [12], and Bayala, et al. [13], particular components such kaempferol, oxygenated terpenes, sesquiterpene hydrocarbons, and monoterpene hydrocarbons are responsible for the leaf extract's anticancer effects.

Alchornea cordifolia (christmas bush)

According to a study by Kuete, et al., [14], the activation of caspase, damage to the mitochondrial membrane, and production of reactive oxygen species (ROS) were some of

the mechanisms used by *Alchornea cordifolia*'s methanolic leaf extract to cause cell death in adriamycin-sensitive leukemia (CCRF-CEM) cells. Furthermore, it was shown that CCRF-CEM cells were negatively impacted by the methanolic bark extract of *A. cordifolia*. *Alchornea cordifolia* may have anticancer properties because of the presence of bioactive substances as flavonoids, saponins, cardiac glycosides, steroids, anthraquinone, terpenes, xanthenes, alkaloids, and tannins [15].

Allium sativum (garlic)

The effectiveness of *Allium sativum* and its organosulfuric components in preventing the development of breast, larynx, colon, skin, uterine, esophageal, bladder, and lung cancers has been demonstrated in several research [16-18].

It has been discovered that the main ingredient in *Allium sativum*, allicin, has anticancer characteristics that can fight both breast [19] and gastrointestinal cancer [20]. Apoptosis, or programmed cell death, is started as part of its anticancer function [19-21]. When *Allium sativum* is broken down or chopped, allicin 1 is transformed into allicin 2 by an enzyme. Human cancer cell growth is successfully stopped by allicin [22]. Another substance found in *Allium sativum* called ajoene prevents leukemia cells from proliferating and initiates apoptosis, or programmed cell death [23].

Numerous studies have looked at the possible effects of this substance on particular cancer types, including Colorectal, esophageal, gallbladder cancers [24-26].



Figure 2: When the garlic plant is assaulted or hurt, an enzyme reaction results in the production of allicin. Toxic to insects and microbes, the chemical alliin is converted by the enzyme alliinase to allicin [27].

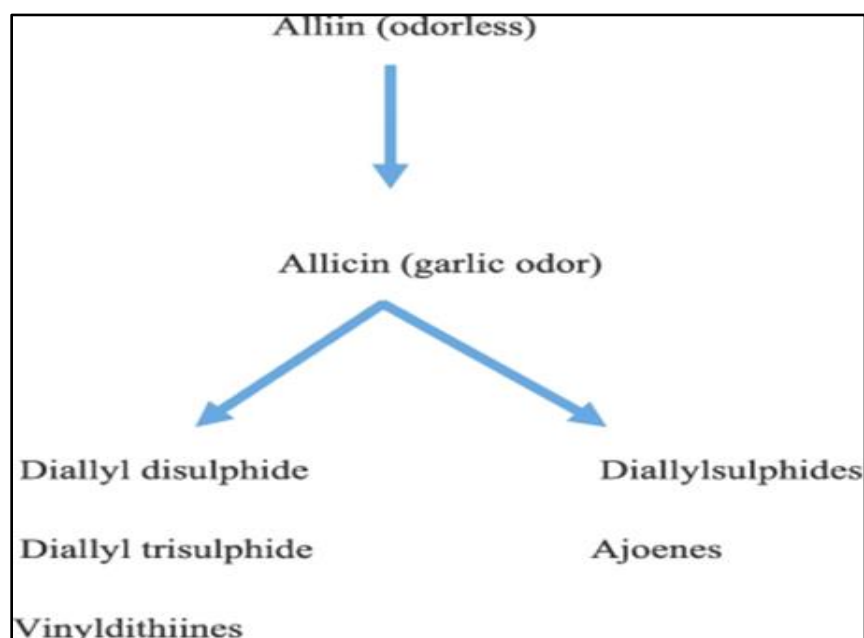


Figure 3: Action of allicin on tumor [28].

Allicin, a sulfur molecule produced from garlic, has been shown to block ornithine decarboxylase, an oncogenic enzyme that stimulates the development of neoplastic cells by elevating polyamine levels [29,30]. Allicin and cyclophosphamide together revealed anticancer effects in a different trial. The SH-SY5Y NB cell line was transplanted into BALB/c-nu/nu mice for the study. Allicin (10 mg/kg/day) and cyclophosphamide treatment together lowered tumor size, reduced tumor cell proliferation, increased mouse survival rate, boosted CD4+, CD8+,

and NK cell levels in serum, and increased levels of IFN- γ [31].

Z-ajoene, a naturally occurring chemical produced from garlic, was studied for its antitumor properties by Li, et al., [32]. Z-ajoene has an IC₅₀ value of 25 μ M in vitro, and it was shown to reversibly impede the assembly of microtubule proteins. Z-ajoene inhibited tumor development in vivo, lowering it in mice with sarcoma 180 and hepatocarcinoma 22 by 38% and 42%, respectively. In both laboratory and live animal settings, this study found that Z-

ajoene significantly inhibited the proliferation of tumor cells. Z-ajoene appears to have a number of targets, including the microtubule cytoskeleton, however the ways in which it interacts with microtubules differ from those of other microtubule poisons, including the Vinca alkaloids.

Using the human NB cell line LA-N-5, Welch, et al., [33] assessed the anticancer impact of S-allylcysteine (SAC). For eight days, the cells were exposed to SAC at different doses (200, 400, 800, and 1600 g/mL). The results showed that cell proliferation started to decline at a concentration of 400 g/mL, suggesting that SAC may have antiproliferative characteristics. However, the therapy failed to cause differentiation of the NB cells, as determined by the analysis of morphological, biochemical, and molecular markers.

Karmakar, et al., [34] conducted a study on SH-SY5Y cells to examine the effects of diallyl sulfide (DAS) and diallyl disulfide (DADS) on intracellular calcium levels and cell death. Treatment with DAS and DADS resulted in increased intracellular calcium levels, causing endoplasmic reticulum stress.

Kanamori, et al., [35] a more recent study, examined the effects of SAC on the SJ-NK-P and IMR5 NB cell lines. The investigation found that SAC affected the potential of the mitochondrial membrane. Treatment with 1 and 2 mg/mL of aged garlic extract (AGE) caused a drop in the chemical gradient (pHm) and a drop of up to 120 mV in the mitochondrial membrane potential (m). Increased glutathione oxidation, lower levels of reduced glutathione, an increase in apoptotic cells, and G₁ phase cell cycle arrest were all associated with these alterations.

Ammi majus (queen anne's lace plant)

Studies have shown that the ethanol extract of this plant is harmful to HeLa and MCF7 cells. The plant's primary coumarin chemicals, which are members of the phenol compound family, have been linked to its key biological functions. The cytotoxic effects of coumarin compounds on cell lines and their capacity to cause apoptosis to have been established by prior studies. Psoralens, a prominent coumarin component present in this plant, have been shown to have anticancer effects via blocking cytochrome p450 activity.

HepG2 cells were used in research by Issa, et al., [36] to examine the results of xanthotoxin at a concentration of 6.9 g/mL. The findings showed significant changes to the DNA-cell cycle, which were shown as a rise in apoptotic pre-G₁ and G₂/M stages and a reduction in the S-phase. Additionally, xanthotoxin significantly increased the number of HepG2 cells that were Annexin-V positive in the early and late phases of apoptosis.

In addition, compared to control cells, there was a considerable decrease in autophagic flux in cancer cells. Xanthotoxin exhibits a strong interaction with the amino acid Asp479 in topoisomerase II (PDB code: 3QX3), which is a DNA-relaxing enzyme, much like the co-crystallized inhibitor (etoposide). These results imply that xanthotoxin could have broad-spectrum anticancer properties. The study also showed that xanthotoxin has anticancer activities and is well-tolerated by healthy human cells. To maximize its anticancer effectiveness, toxicity, solubility, and pharmacokinetics, more research is necessary.

Ammi visnaga (khella plant)

According to Kamal, et al., [37] study from 2022, butanoic acid, 2-methyl-, pentyl ester, (Z)-ocimene, D-limonene, linalool, pulegone, and lavandulyl-butyrate are the main ingredients in *Ammi visnaga* L. essential oil. The DPPH and reducing power experiments revealed that the oil has moderate to low in vitro free radical scavenging activity. The number of polyphenols in the oil was strongly linked with its antioxidant capacity.

At doses of 600 and 1200 mg/kg, the essential oil of *Ammi visnaga* L. displayed strong antioxidant activity in vivo. It was shown to considerably lower lipid peroxidation while significantly increasing the levels of catalase, superoxide dismutase, and reduced glutathione. These findings led Kamal, et al., [37] to the conclusion that *Ammi visnaga* L. could be a source of compounds with antioxidant potential for the protection of illnesses associated with free radicals.

Arafah, et al., [38] used 500, 1000, and 1500 g/ml based on IC₅₀ values to evaluate the cytotoxic and apoptotic effects of *A. visnaga* seed extract on the human liver cancer cell line (HuH-7) in their investigation. After 48 hours of treatment, the MTT test showed that cell viability was dramatically decreased at dosages of 1000 g/ml and above. At dosages of 1500 and 2000 g/ml, the NRU test revealed a dose-dependent increase in lysosomal toxicity. Using SOD, glutathione (GSH), catalase, and ROS tests, the authors evaluated the degree of oxidative stress-mediated cytotoxicity.

The HuH-7 cells' mitochondrial membrane was proven to have been damaged by the loss

of mitochondrial membrane potential (MMP), according to the data, which also showed a large rise in intracellular ROS. After therapy, GSH levels dramatically rose whereas SOD and catalase levels and activity sharply dropped. Additionally, compared to the control, it was seen that the effects of MMP were diminished following therapy. Finally, the scientists observed that the gene expression data showed a considerable increase of apoptotic genes.

Visnagin, a naturally occurring furanochromone derivative derived from *Ammi visnaga*., was studied by Aydogmus-Ozturk, et al. [13] to see whether it has any possible anticancer properties against malignant melanoma (HT 144) cell lines. Visnagin's ability to produce singlet oxygen was assessed using the RNO bleaching procedure, and its cytotoxic activity was evaluated using the MTT test. Additionally, to examine the cytotoxic activity under illumination, visnagin-treated HT 144 cells were subjected to visible light (400 nm) for 25 minutes.

Using flow cytometry and the annexin V/PI dual labeling approach, the researchers quantified the effect of visnagin on apoptosis. They also looked at the role of TNF-production in apoptosis. In a typical MTT experiment, visnagin has an 80.93% inhibitory activity against the HT 144 cancer cell lines at a dose of 100 g/mL. At the same dose, it had less inhibitory action (63.19%) in the illuminated MTT test. Additionally, the researchers discovered that visnagin produced intracellular reactive oxygen species (ROS), which in turn caused apoptosis, and that it had a 25.88% apoptotic impact on the HT 144 cell lines.

Arctium lappa (greater burdock plant)

In order to determine the active ingredients in *A. lappa* root extracts and their effectiveness against cancer cells, Gurunanselage Don, et al., [39] undertook a study. The chemicals were recognized by LC-ESI-MS. In Jurkat T cells after 24 hours, the ethyl acetate root extract was shown to be the most effective, with an IC₅₀ value of 102.2 42.4 g/ml. None of the extracts were harmful to 3T₃ cells, showing that they were only effective against cancer cells. Both ethanolic and ethyl acetate root extracts significantly altered the morphology of Jurkat T cells, resulting in cell shrinkage, cell death, and separation from neighboring cells. Additionally, the treated cells had elevated caspase 3/7 activity as well as modified mitochondrial membrane potential.

Inducing DNA fragmentation in Jurkat T cells only the ethyl acetate root extract at IC₅₀. Only 6 of the 8 compounds found by the LC-ESI-MS study had been documented to have diverse biological functions. According to these findings, the ethyl acetate extract of *A. lappa* promotes intrinsic apoptosis by activating caspase 3/7 and decreasing the potential of the mitochondrial membrane and possesses strong anticancer capabilities.

The ethyl-acetate fraction (EAF) was found to have antiproliferative effect, according to Machado, et al., [40] Onopordopicrin (1), a mixture of 1 with dehydromelitensin-8-(4'-hydroxymethacrylate) (2), a mixture of 2 with dehydromelitensin (3), a mixture of 1 with melitensin (4), dehydrovomifoliol (5), and loliolide (6) were then isolated from the EAF using sequential column chromatography over silica gel. Utilizing spectroscopic

techniques like NMR and MS as well as comparisons to published data, the chemicals were identified. The compounds' Caco-2 cell CC₅₀ (g/mL) values were determined as follows: 1: 19.7 3.4, 1 with 2: 24.6 1.5, 2 with 3: 27 11.7, 1 with 4: 42 13.1, and 6: 30 6.2.

Using HRESI-MS and a comparison to earlier data, Predes, et al., [41] were able to identify arctigenin, quercetin, chlorogenic acid, and caffeic acid in their investigation. The only extracts that shown efficacy against cancer cell lines, especially the K562, MCF-7, and 786-o cell lines, were those made from dichloromethane. The Soxhlet extraction had the largest phenolic content, according to the authors, whereas the hydroethanolic extracts had the highest free radical scavenging activity. Additionally, the K562, MCF-7, and 786-o human cancer cell lines were specifically inhibited from proliferating by the dichloromethanic extracts.

Artemisia absinthium (common wormwood plant)

Artemisia extract was proven to have antioxidant effects, following Konyuncu, et al., [42] study. Chlorogenic acid was shown to be the most prevalent phenolic component, followed by quinic acid, cinnamic acid, rhoifolin, and malic acid. The study used LC-MS/MS for content analysis and discovered the existence of various phenolic components. While the effect on HEK-293 cells was negligible, in vitro studies on the cancer cells DLD-1 and ECC-1 demonstrated cytotoxic effects of *Artemisia* extract. The research showed that *Artemisia* extract raised the quantities of free radicals inside cancer cells, causing DNA damage and eventually leading to apoptosis. The text that has been

paraphrased still includes all necessary sources.

Cell survival tests were performed by Shafi, et al., [43] to see how *Artemisia absinthium* (AA) affected MDA-MB-231 and MCF-7 cells. The findings showed that AA was cytotoxic to both cell lines, and morphological characteristics such DNA staining and the accumulation of the sub-G1 peak suggested that the extract induced apoptosis. While 20 g/mL AA exposure caused a time-dependent elevation of Bcl-2 protein in MDA-MB-231 cells, 25 g/mL AA treatment activated caspase-7 and elevated Bad in MCF-7 cells. Following AA treatment in both cell lines, MEK1/2 and ERK1/2 were both inactivated in a time-dependent manner.

Inhibitory effects of various extracts on various cancer cell lines were observed, according to Taghizadeh Rabe, et al., [44]. With IC₅₀ values of 35 and 60 g/ml, respectively, the dichloromethane and methanol extracts of *A. ciniformis* Krasch. & Popov ex Poljak. had the most growth-inhibitory effects on AGS cells. It was discovered that *Artemisia diffusa* Krasch. ex Poljak. dichloromethane (IC₅₀ value: 71 g/ml) and *A. ciniformis* ethylacetate (IC₅₀ value: 73 g/ml) extracts were more potent against HeLa cells.

Astragalus cytosus

Wu, et al., [45] examined the interactions between apatinib and astragalus polysaccharide (AsPs) on gastric cancer AGS cells. According to the study, VEGFR-2 was expressed by the human gastric cancer line AGS. When combined, Apatinib and AsPs had stronger inhibitory effects on cell proliferation, migration, and invasion than

either drug alone did. Both drugs suppressed AGS cell proliferation in a dose-dependent manner. Furthermore, apoptosis was significantly boosted by the addition of AsPs and was further promoted by apatinib therapy.

According to Wu, et al., [45], the combination of apatinib and asPs suppressed the production of MMP-9 and phosphorylated AKT (p-AKT). Cellular autophagy was activated by apatinib both alone and when combined with AsPs, and it could be reduced by the autophagy inhibitor 3-MA. Further activation of apoptosis and inhibition of cell growth were caused by the reduction of autophagy.

According to Li, et al., [46], astragalus therapy significantly slowed the development of the H22 carcinoma, with inhibitory rates ranging from 17.28% to 52.36%. When compared to the control group, astragalus administration substantially enhanced the rate of cell death, raised protein expression of Bax, and decreased the Bax/Bcl-2 ratio in tumors from H22 transplants, according to flow cytometry (FCM) and immunohistochemistry analyses (P 0.05). Bcl-2 protein expression was also considerably lower in the astragalus-treated group than in the control group (P <0.05) in comparison.

The anticancer impact of *Astragalus saponins* was examined in research by Auyeung, et al. [47]. The outcomes demonstrated that AST therapy caused overexpression of NAG-1, which then caused PARP breakage and apoptosis. Gene expression, Egr-1 expression, and DNA binding activity all increased in correlation with the activation of the NAG-1 promoter. AST-induced NAG-1 activation was

enhanced by co-treatment with the PI3K inhibitor LY294002 or the Akt inhibitor, but the effect was abolished by NAG-1 siRNA transfection. The ERK inhibitor PD98059 did not have an impact on how much NAG-1 induction was induced, though. These results imply that NAG-1 could be a possible molecular target of AST in its antitumorigenic and proapoptotic activities, and that it might have additive effects when combined with PI3K-Akt inhibitors.

Astrodaucus orientalis

The human breast cancer cell line T47D was used in a study by Abdolmohammadi, et al., [48] to examine the antiproliferative properties and mechanism of cell death of *Astrodaucus orientalis*. To assess the antiproliferative impact and analyze changes in the cell cycle pattern, the researchers used the MTT test and the DAPI reagent. The Annexin V/PI technique was used for the analysis of apoptosis. By analyzing changes in their gene and protein expression using RT-PCR and immunocytochemistry methods, the study further investigated the roles of p53 and Bcl-2 in carcinogenesis and cell death. On the T47D cells, the aerial and root extracts both displayed potent antiproliferative activities. While the aerial extract caused cell cycle arrest in the G2/M phase, the root extract exhibited a pattern that was comparable to RPMI. The root extract had a less noticeable impact than the aerial extract, although both extracts caused apoptosis. The extracts reduced the expression of the p53 gene, but Bcl-2 gene expression was undetectable. Additionally, the expression of the proteins p53 and Bcl-2 was decreased by both extracts.

Avicennia marina (grey mangrove, white mangrove plant)

The anticancer and anti-proliferative properties of *Avicennia marina* plant extracts were studied by Albinhassan, et al., [49]. On the cell lines HCT-116, HepG2, and MCF-7, the hexane extract showed modest apoptotic induction but a strong inhibitory impact. Illian, et al., observed cell cycle inhibition and apoptosis induction when WiDr cells were exposed to polyisoprenoid extracts from *A. marina* and *A. lanata* leaves.

After separating secondary metabolites from *A. marina* leaves, Huang, et al., [2] discovered that they have strong anticancer properties, especially in the ethyl acetate extracts, which slowed the development of tumors in a breast cancer xenograft model. The study by Momtazi-Borojen, et al., [50] concentrated on luteolin, an active component of the crude methanol extract from *A. marina* that triggered apoptosis in breast cancer cells through controlling the p53 and Bcl-2 pathways.

Boswellia serrata (indian frankincense plant)

Ahmed, et al., [51] examined the cytotoxic effects of several *Boswellia serrata* oleo-gum resin fractions and volatile oils on HepG2 and HCT 116 cell lines. The main substances in the lipoidal matter of the resin were identified as tricosane, cholesterol, stigmasterol, and -sitosterol. Pent-2-ene-1,4-dione, 2-methyl-levulinic acid methyl ester, and methyl-1-methylpentadecanoate were also detected in the chromatographic fractions. Sabinene, terpinen-4-ol, and terpinyl acetate were the main components of the volatile oils. With IC₅₀ values similar to those of doxorubicin

and 5-fluorouracil, extracts 1 and 2 demonstrated substantial cytotoxic action against both cell lines.

According to the study, oleo-gum resin extracts from *Boswellia serrata* may have the ability to kill liver and colorectal cancer cells.

Camellia sinensis (tea plant)

In 1995 research by Yasumoto, et al., [52], it was discovered that green tea is made with little oxidation from the young buds and petals of the tea plant and that it naturally includes antioxidants, caffeine, theophylline, and thianin. According to research done on rats, green tea may suppress the activity of the 5-alpha reductase enzymes, which turn testosterone into dihydrotestosterone, a substance linked to prostate cancer and a known carcinogen. Consequently, green tea may prevent prostate cancer from spreading.

The cytotoxicity of *Camellia sinensis* extract was assessed on Caco-2 and L929 cells in different research by Esghaei, et al., [53]. The MTT assay was used to examine the extract at various doses, and immunofluorescence microscopy was used to evaluate the aquaporin 5 (AQP5) protein, a biomarker for cell survival. The outcomes showed that, at a concentration of 800 g/ml (P 0.05), the hydroalcoholic extract of green tea greatly slowed the proliferation of Caco-2 cells while having no effect on L929 cells. Additionally, after being exposed to the green tea extract in Caco-2 cell culture, the levels of the AQP5 protein dropped. These results suggest that green tea extract may have potential anti-cancer effects on Caco-2 cells, possibly through modulating the expression of the AQP5 protein.

Cimicifuga racemosa (black cohosh)

In research by Shareef, et al., [54], it was discovered that breast cancer patients frequently took black cohosh during radiation and chemotherapy. Native Americans have long utilized this plant to treat menopausal symptoms, premenstrual pain, and dysmenorrhea. Furthermore, it is acknowledged to possess characteristics similar to those of abortion. of the nineteenth century, black cohosh served as the primary ingredient of Lydia Pinkham's Vegetable Compound, a well-known patent medication. Today, a variety of black cohosh formulations are sold in pharmacies and have been demonstrated by herbalists to be secure and efficient for treating menopausal symptoms.

Citrullus colocynthis (colocynth plant)

The inhibitory effects of phycocyanin and *C. colocynthis* extract on cancer cells were compared to a control, according to Hamdan, et al., [55]. Higher inhibitory effects were seen with extract plus phycocyanin and *C. colocynthis* extract than with phycocyanin alone. Phycocyanin and extract alone both had IC₅₀ values of 6.2 0.86 and 3.8 1.06 g/L against ViDr, but *C. colocynthis* extract and the combination had IC₅₀ values of 6.90 1.11 and 5.87 3.43.

Additionally, these therapies showed no cytotoxicity toward healthy cells. The researchers found that the expression of the Bax gene was markedly elevated after exposure to extract+phycocyanin and *C. colocynthis* extract. Additionally, the expression of the caspase 3 gene was considerably elevated in CRC cell lines when extract+phycocyanin and *C. colocynthis* extract were combined [55].

The anticancer properties of *C. colocynthis* were reviewed by Abdulridha, et al., [56], and it was discovered that these properties can be related to multiple mechanisms. The review brought attention to the fact that *C. colocynthis* triggers apoptotic pathways by elevating caspase-3 and decreasing STAT3 activity.

Additionally, TNF- α , nitric oxide, and pro-inflammatory cytokines including IL-6, IL-8, and IL-1 are affected by the antioxidant and anti-inflammatory characteristics of *C. colocynthis*. Additionally, the plant has antiangiogenic and antimetastatic properties and suppresses the Wnt/-catenin signaling pathway [56].

***Citrus aurantifolia* (key lime)**

Citrus aurantifolia has proven many anticancer properties, according to Zhao, et al., [57]. Inhibiting the advancement of the tumor cell cycle, especially during the S-phase, and activating the release of caspase-3, which promotes apoptosis, have both been seen. Additionally, it has been demonstrated that *C. aurantifolia* increases the quantity of tumor infiltrating CD8+ T lymphocytes, increasing the immune response against cancer cells. Additionally, it has been shown that *C. aurantifolia* inhibits the apoptosis-inhibiting proteins BclxL and Mcl-1.

Polymethoxyflavones, which are present in the aqueous extract of *C. aurantifolia*, have been demonstrated to reduce cancer cell metastasis by preventing cell adhesion and invasion. These bioactive substances also encourage the release of natural killer (NK) cells, which causes cancer cells to be destroyed. The activity of cyclin-dependent

kinases (Cdk) has also been discovered to be suppressed by *C. aurantifolia*, which limits the advancement of the tumor cell cycle in the G₁-phase [50]. Notably, breast MDA-MB-453, pancreatic Panc-28, and colon SW-480 cancer cells all showed inhibition of growth in response to *C. aurantifolia* extract [58].

***Crocus sativus* (autumn crocus)**

The Iridaceae family includes the perennial plant species *Crocus sativus*. It has been discovered that saffron, which is made from the plant's stigma, possesses anticancer effects. According to several studies, saffron extract promotes apoptosis in human cancer cells, prevents DNA synthesis, has lethal effects on colorectal and breast cancer cells, and has anti-angiogenic properties. It also inhibits DNA synthesis. Saffron is harmful to normal cells; thus, it should be used with caution when consumed in excessive concentrations. Several studies reveal that saffron extract possesses apoptogenic effects and may be used as a chemotherapeutic agent to treat cancer [59-63].

***Curcuma longa* (turmeric)**

Numerous clinical trials have demonstrated the usefulness of curcumin, a key component of turmeric, in the prevention and treatment of ovarian cancer [64]. Curcumin has been demonstrated to have anticancer properties against many malignancies [4]. Many illnesses, including cancer, are significantly influenced by free radicals and other hazardous byproducts of oxidative stress, and curcumin possesses antioxidant properties that lessen or prevent free radical damage [65].

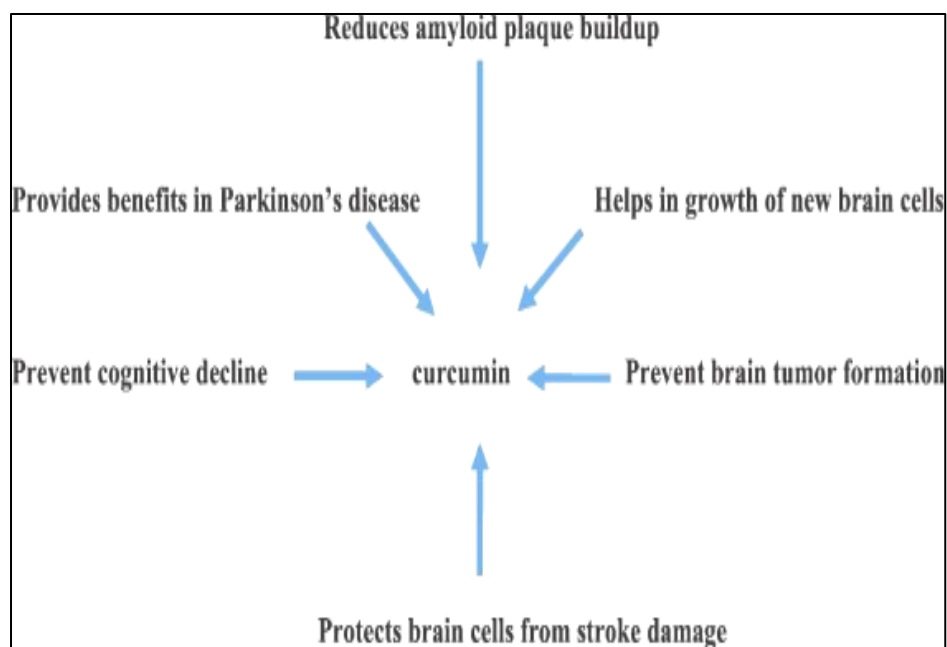


Figure 4: Activities of curcumin [28].

It has been demonstrated that the natural substance curcumin, which is present in turmeric, has inhibitory effects on all stages of cancer growth, including initiation, promotion, and propagation. Curcumin also inhibits nitrosamine synthesis and boosts the body's inherent antioxidant defenses. Additionally, it raises glutathione and other non-protein sulfhydryl levels, which directly affect a number of enzymes implicated in the development and spread of cancer [7].

Echinacea (coneflower)

The Asteraceae family includes the plant echinacea, which is mostly found in North America and Europe. *Echinacea purpurea*, *Echinacea angustifolia*, and *Echinacea pallida* are the most often utilized species for herbal medicines, with *E. purpurea* being the most well researched. It is also known by other

names, including black Sampson, Kansas snakeroot, and purple coneflower.

According to studies, *E. purpurea* can increase the number of mice's natural killer cells and has the potential to be used as a cancer treatment. Echinacea contains flavonoids that act as immunological stimulants by encouraging lymphocyte activity, macrophage phagocytosis, natural killer cell function, and interferon production. Echinacea has also shown promise in extending the lives of cancer patients who are at an advanced stage of the disease. Commercial Echinacea formulations have been demonstrated to boost macrophage cytokine production, while the effects on T-cell and B-cell activation are not well known. Echinacea's immunomodulatory properties are a result of a number of its chemical components [66].

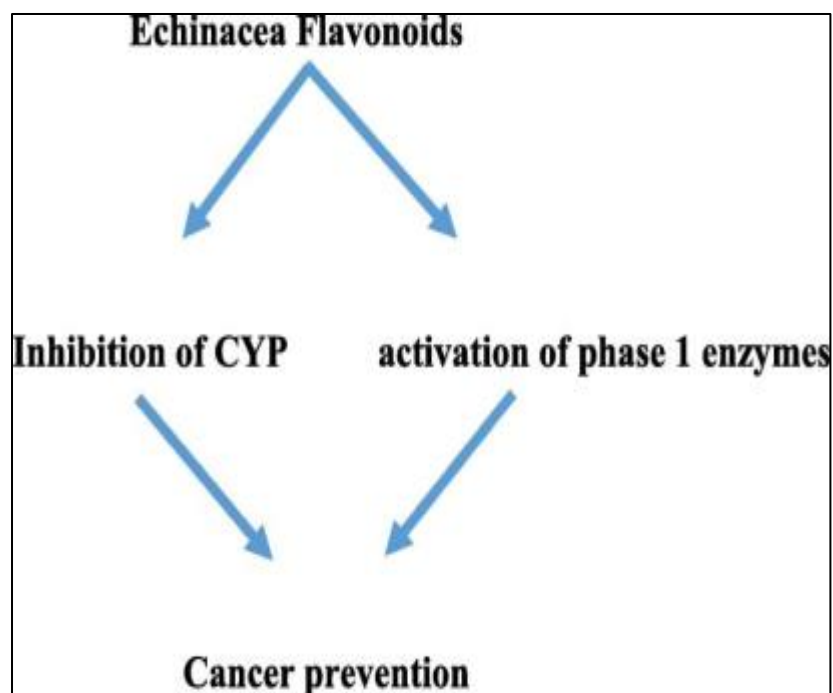


Figure 5: Action of flavonoids for cancer prevention [28].

Ferula assa-foetida (hing spice)

In their investigation of the effects of the ethanolic extract of *Ferula assa-foetida* on the survival of PC12 and MCF7 cells, Abroudi, et al., [67] found that cell viability was significantly reduced. According to their research, the IC₅₀ values for MCF7 cells were 1.30 M, 1.284 M, and 0.753 M, respectively, at 24, 48, and 72 hours of exposure. According to Abroudi, et al., [67], the equivalent IC₅₀ values for PC12 cells were 2.84 M, 0.8 M, and 0.4 M.

Shafri, et al., [43] found that varied doses of the extract over 24 and 48 hours resulted in decreased cancer cell survival while examining the effects of methanolic and ethanolic extracts of *Ferula assa-foetida* resin on an osteosarcoma cell line. According to Shafri, et al., [43], the concentration of 20 mg at 48 hours produced the most prominent impact, with effect rates of 29.5% for the

ethanolic extract and 35.2% for the methanolic extract. These results suggest that the ethanolic extract has a better capacity to cause the death of cancer cells [43].

Mosaddegh, et al., [68] investigated the effects of extracts from *Ferula assa-foetida* utilizing petroleum benzene, chloroform, and methanol on a number of cell lines, including MCF7, HepG2, A549, HT-29, and MDBK. According to Mosaddegh, et al., [68], the petroleum and chloroform extracts had IC₅₀ values below 52 g/mL across the four cell lines, but the methanol fraction had an IC₅₀ value greater than 100 g/mL. Particularly, the petroleum fraction had an IC₅₀ of 45.73 g/mL in MCF7 cells whereas the chloroform fraction showed an IC₅₀ of 61.42 g/mL.

Ficus benjamina (weeping fig)

According to Rastogi, et al., [69], *Ficus* species contain a variety of chemical

substances, including triterpenoids like oleanolic acid, ursolic acid, protocatechuic acid, and maslinic acid, alkaloids, phenolic acids, steroids, saponins, and coumarins. Phenolic substances, flavonoids, and vitamin C make up the non-enzymatic components. Ascorbate oxidase, ascorbate peroxidase, catalase, and peroxidase are among the components of enzymes. The antioxidant capacities of various *Ficus* species have also been researched [70].

Obafemi, et al., [70] offered sufficient data in their review to back up their claim that *Ficus benjamina* might be a strong contender in the fight against cancer. According to Obafemi, et al., [71], the extract of *Ficus benjamina* showed specific cytotoxicity toward HEK293T cells while having no effect on normal cells.

The extract, according to Obafemi, et al., [71], showed a better therapeutic index than the anticancer medication Bortezomib. Their findings reveal that Bortezomib significantly ($p > 0.05$) outperformed in suppressing human embryonic kidney (HEK293T) cells. *F. benjamina* supported the healthy cells more.

***Linum usitatissimum* (flax seed)**

The effects of flaxseed lignan derivatives on various types of acute myeloid leukemia (AML) cancer cells were investigated by Tannous, et al., [72]. Enterolactone (ENL), one of these derivatives, showed the most encouraging outcomes by having a notable and focused cytotoxic effect on AML cell lines while sparing normal cells. An increase in Annexin V staining in AML cells exposed to higher concentrations of ENL was used as evidence that the observed cytotoxic effects were caused by the induction of apoptosis. Furthermore, a cell death ELISA analysis

confirmed cellular and DNA fragmentation, and a cell cycle distribution analysis showed an increase in the proportion of cells in the pre-G phase. Further proof that the intrinsic apoptotic pathway was activated after ENL treatment came from a Western blot analysis of protein expression. In addition, these effects were accompanied by an increase in the production of reactive oxygen species (ROS) within the cells.

***Ocimum gratissimum* (african basil)**

Ocimum gratissimum has shown promising anticancer action, particularly with 3, 4-dihydroxycinnamic acid which is also called caffeic acid and oleanolic acid. While oleanolic acid from the ethanolic leaf extract of *O. gratissimum* inhibited breast cancer cell lines, as well as lung cancer cell lines prostate cancer, colon, pancreatic, and renal carcinoma. Caffeine from *O. gratissimum* has been found to suppress the HeLa cervical cell line [73]. Likewise, *O. gratissimum*'s crude extract was shown to limit tumor growth and decrease the emergence of breast cancer [70].

According to Lin, et al., [74], the aqueous extract of *O. gratissimum* inhibits the growth of osteosarcoma cells and bone cancer in humans as well as the A549 cell line. Saponins, linalool, eugenol, geraniol, alkaloids, thymol, and citral are other bioactive components in *O. gratissimum* that may have anticancer effects [75].

***Pegauum harmala* (wild rue, syrian rue, african rue)**

Perennial herb *Peganum harmala*, a member of the Zygophyllaceae Nitrariaceae family, is most frequently found in dry Mediterranean areas including North Africa, Turkey, and

Syria. It has green leaves with slender, water-filled divisions that reach a height of between 30 and 50 cm. Large blooms with prominent petals and greenish-white sepals are produced by the shrub. According to studies, this plant's extract has the power to reduce the viability of epithelial cervical cancer cells and colon carcinoma cells. Alkaloids, which have anticancer characteristics, are the main components of *Peganum harmala*. The antioxidant properties of these alkaloids against human breast cancer cells have been further demonstrated by chemical analysis [76].

Physalis alkekengi (chinese lantern)

A perennial herbaceous plant with potato-shaped corners and creeping rhizome stems is called *Physalis alkekengi*. According to research, the plant's aqueous extract reduces the cytotoxicity of U937 cells. Studies have revealed that the triterpenoid-based primary constituents of *Physalis* plants, including the physalins B and M, exhibit anticancer cytotoxic effect against cancer cells, notably the HeLa human cell line and the SMMC-7721 and HL-60 cell lines from the hepatum [77].

Polygonum aviculare (prostrate knotweed)

The *Polygonum* genus contains the Polygonaceae plant family of the Caryophyllales order. The *Polygonum aviculare* is an evergreen plant with a 50-centimeter-long stem, tiny, pointed leaves, and tiny, pink flowers. The possible inhibitory effects of the plant extract on cancer cell growth have been demonstrated in a number of investigations. For example, the HeLa cancer cell line was reported to be reasonably inhibited by the extract [78].

The plant extract produced cytotoxicity and promoted apoptosis in breast cancer cells (MCF7). Alkaloids, flavonoids, and tannins are this plant's primary chemical constituents [79]. Studies on the plant's anticancer effects have revealed that, despite the existence of phenol chemicals, the benefits are mostly attributable to other parts of the plant [78].

Rosa damascenes (damask rose)

The callus growth characteristics and secondary metabolite contents in *R. damascena* were greatly enhanced by L-ascorbic acid treatment, according to Darwish, et al., [80]. Comparing the L-ascorbic acid-treated group to the citric acid-treated and control groups, the IC₅₀ value in the L-ascorbic acid-treated group was much lower (137 ug/mL). In addition, the *R. damascena* callus that was evoked had substantial anti-proliferative, anti-clonogenic, and anti-migratory actions on Caco-2 cancer cells, suggesting its potential as an adjuvant anti-cancer treatment.

Thymbra spicata

According to Khalil, et al., [81], *T. spicata*'s ethanolic extract dramatically reduced the growth of many human tumor cell lines while having no effect on non-neoplastic cells. On the human breast cancer cell line MCF-7 and the normal breast cell line MCF-10A, more research into the molecular mechanism underlying the extract's in vitro anticancer activity was carried out. Reactive oxygen species (ROS) formation, nitric oxide release, apoptosis induction, and a decline in STAT3 and NF-κB phosphorylation were all associated with the effects on MCF-7 cells. In order to lessen negative side effects and drug resistance, ethanolic extract from *T. spicata*

leaves may be employed as a new therapeutic agent in conjunction with traditional chemotherapy.

Thymus vulgaris (thyme)

Thymus vulgaris essential oils were discovered to have chemo preventive and therapeutic activities against experimental breast cancer in a study done by Kubatka, et al., [82]. In rat cancer cells, treatment with these essential oils led to a reduction in the expression of CD44 and ALDH1A1 and an increase in the expression of Bax. The expression of VEGFR-2 and malondialdehyde levels were also decreased in rat carcinomas treated with *T. vulgaris* essential oils.

A drop in lysine methylation status, an up-regulation of certain microRNAs (miR22, miR34a, and miR210), and a substantial decrease in the methylation status of four gene promoters were all seen in the study's examination of epigenetic modifications in rat tumors. Breast cancer cell lines MCF-7 and MDA-MB-231 were used for in vitro tests, and the results showed that *T. vulgaris* essential oils had antiproliferative and proapoptotic properties.

In a different study conducted by Al-Menhali, et al., [83], it was shown that *Thymus vulgaris* extract (TVE) had concentration- and time-dependent inhibitory effects on the growth of colon cancer cells. Increased caspase3/7 activity revealed that the inhibitory impact was linked to an increase in apoptotic cell death. In addition, HCT116 cells' abilities to migrate and invade were considerably decreased by TVE, which raises the possibility that TVE might prevent the malignant phenotype of colon cancer cells. Some of the bioactive substances found in TVE, according

to the researchers, may be useful in treating human colorectal cancer.

Urtica dioica (common nettle)

The possible antitumoral effects of *Urtica dioica* in the treatment of breast cancer were looked at in research by Karakol, et al., [84]. *U. dioica* showed cytotoxicity against three distinct breast cancer cell lines, and it also caused apoptosis, as shown by a rise in the number of cells that were Annexin-positive. Rat in vivo experiments also showed that treatment with *U. dioica* raised the production of caspase 3, p53 protein, and TUNEL positive cells, indicating increased apoptosis. Additionally, there was a decrease in the expression of the proliferation marker Ki-67 in the therapy groups. The study also showed that rats treated with *U. dioica* had much less tumor volume than rats in the control group.

An aqueous extract of *Urtica dioica* leaf was reported to have dose-dependent anti-proliferative effects exclusively on MCF-7 breast cancer cells after 72 hours in different research by Fattahi, et al., [85], with an IC50 value of 2 mg/mL.

DNA fragmentation, apoptotic cells identified by flow cytometry analysis, and an increase in the levels of proteins involved in the apoptotic pathway, such as calpain 1, calpastatin, caspase 3, caspase 9, Bax, and Bcl-2, were all indicators of this anti-proliferative activity's association with increased apoptosis. The promise of *Urtica dioica* as a homeopathic treatment for breast cancer is highlighted in this study, which also offers the first proof of the herb's in vitro anti-proliferative impact on a breast cancer cell line.

Viola tricolor (wild pansy)

A violacein-producing Antarctic bacterial strain's production and possible applications were examined in research by Alem, et al., [86]. The scientists discovered that violacein has antiproliferative effects in several cell types. Survival tests showed that the pure pigment had antiproliferative properties and made HeLa cells more sensitive to the chemotherapeutic medication cisplatin. On the basis of micronucleus studies, the pigment did not, however, have the genotoxic effects that were anticipated in HeLa cells.

Sagdehnia, et al., [87] examined the possible anticancer potential of *Viola tricolor* in another study. While displaying negligible toxicity to healthy murine fibroblast L929 cells, the ethyl acetate fraction of *V. tricolor* had the highest effectiveness, notably against MCF-7 cells. The increase in the sub-G₁ peak of cells stained with propidium iodide, as well as the elevation of the Bax/Bcl-2 ratio and levels of cleaved caspase-3, provided the researchers with more evidence that the ethyl acetate fraction promoted apoptosis. The ethyl acetate fraction also reduced the diameter of capillaries on the chorioallantois membrane, which further reduced angiogenesis. Six significant peaks with various retention durations were found by HPLC fingerprint analysis in the ethyl acetate fraction. These results indicate that *V. tricolor* induces apoptosis and inhibits angiogenesis, which may have anticancer effects.

Zingiber officinale (ginger)

The cytotoxic properties of *Zingiber officinale* were examined in research by Imade, et al., [88]. With inhibitions of 50% and 43%, respectively, against AU 565 and HeLa cells,

the volatile oil isolated from the rhizome demonstrated strong anticancer activity. The two compounds α-citral and β-citral were found to be the main components of ginger oil. According to the study, *Z. officinale* oil may be effective against cancer.

Another investigation on the antibacterial, antioxidant, and in vitro anticancer properties of *Zingiber officinale* rhizome extract was conducted by Subramani, et al., [89]. Significant antibacterial activity was demonstrated by the extract against several microorganisms. By scavenging free radicals, it also displayed antioxidant activity. In terms of anticancer efficacy, the extract significantly and dose-dependently reduced the growth of MCF-7 breast cancer cells.

The anticancer properties of ginger extract on colon cancer cell lines were studied by Abdullah, et al., [90]. HCT 116 and HT 29 cells' ability to proliferate was decreased by the extract, which in turn caused dose-dependent apoptosis. The cell cycle was likewise stopped by the ginger extract at the G₀/G₁ and G₂/M stages. These results imply that ginger extract may have therapeutic value in the treatment of colon cancer.

Effect of Nigerian spices on cancers

In their study, Alabi, et al., investigated the effect of a recipe derived from various plant species on breast cancer cells in vitro. They formulated two recipes: Recipe A composed of *Anchomanes difformis*, *Garcinia kola*, *Kigelia africana*, and *Xylopia aethiopica*, and Recipe B composed of *Allium ascalonicum*, *Antiaris africana*, *Bridellia scandens*, *Calliandra haematocephala*, *Citrus medica*, *Mangifera indica*, *Nauclea latifolia*, *Tricalysia macrophylla*, and *Trichilia monadelpha*. The

study found that both recipes inhibited cell proliferation by inducing Go/G₁ cell cycle arrest and increasing the expression of apoptotic-inducing proteins, ultimately leading to the death of cancer cells.

Breast cancer as a case study for herbal cancer treatments

Breast cancer treatments are intended to target DNA damage, interfere with cellular integrity, cause apoptotic cell death, and obstruct aberrant cell development pathways, according to Davies, et al., [91]. The majority of breast cancer patients express the estrogen hormone receptor, which causes fast cancer cell growth when circulating estrogens are present. In breast cancers that have the estrogen receptor, the primary goal of current treatments is to break the estrogen reliance.

According to Bright, et al., [92] and Howell, et al., [93] selective estrogen receptor modulators (SERMs), such as tamoxifen, are efficient therapies for breast cancer. Tamoxifen binds to the estrogen receptor, changing its shape to stop the production of estrogen. However, tamoxifen has serious side effects that include a higher chance of second-degree cancers and cardiac issues. Alternative alternatives for endocrine therapy include third-generation aromatase inhibitors, such as anastrozole and letrozole, which reduce the production of estrogen by competitively blocking the aromatase enzyme. It's still not known how AIs will affect the health in the long run. Treatment for breast cancer also works well with growth factor inhibitors, in particular those that target the EGFR receptor. The EGFR is essential for the survival of cancer cells and multidrug resistance. Gefitinib, a small

molecule EGFR tyrosine kinase inhibitor, is helpful in the treatment of breast cancer but has little effect on people with advanced breast cancer. HER2 overexpression is present in around 20% of breast cancer patients, which promotes aggressive disease and decreases survival. At the moment, lapatinib and trastuzumab are drugs that can stop HER2-mediated growth signals. Another method involves anthracycline medicines like doxorubicin attaching to DNA and impeding topoisomerase II activity through enzyme-mediated DNA damage. Anticancer medications like vincristine and vinorelbine interfere with microtubule stability, which results in cell death or mitotic arrest. A microtubule-stabilizing medication called paclitaxel hyperstabilizes microtubule assembly and causes mitotic arrest. These treatment methods come with adverse effects, despite the fact that they have helped to lower breast cancer mortality and increase survival rates. According to Middleton, et al., [94], it is yet unknown if chemotherapy can successfully treat cancer. The treatment comes with a number of hazards and side effects, some of which can be severe and life-threatening, despite the fact that it lowers the chance of recurrence and enhances quality of life in patients with metastatic breast cancer.

Conclusion

Many of these drugs are still in the preclinical or clinical stages of development despite the fact that there is evidence that herbal treatments can successfully treat cancer and its negative effects. As a result, more research is necessary to evaluate these compounds' potential as herbal treatments and to properly translate them into an ideal clinical setting [3].

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