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Medicinal Plants in Combating Breast Carcinogenesis: A Review on Recent Investigations

Sadwal S, Kaur S* and Aniqa A

Department of Biophysics, Panjab University, Chandigarh, India

***Corresponding author:** Dr. Sarvnarinder Kaur, Department of Biophysics, Panjab University, Chandigarh-160014, India, Email: sarvnarinder@pu.ac.in

Review Article

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Abstract

Breast cancer is the most prevalent disease among women and a challenge for the scientific and medical community. Existing treatments for breast cancer are surgery, radiation, chemotherapy, hormone therapy, and targeted therapy. These treatments have the potential to stop the growth and spread of cancer, particularly when the condition is diagnosed at an early stage. As cancer cells reproduce more frequently than the vast majority of normal cells, chemotherapy has a greater chance of successfully killing cancer cells. Certain pharmaceuticals are able to terminate dividing cells by inflicting damage on the section of the cell's control centre that is responsible for the process of cell division. Other medications are capable of interfering with the chemical processes that are necessary for cell division. On the other hand, as cancer is often diagnosed at an advanced stage, in which, the process of curing the disease is extremely difficult. Therefore, it is prudent to prevent the occurrence of this deadly disease. Several researches have consistently found an inverse relationship between cancer and natural sources, including plant extracts, fractions and active components. The synergistic and cumulative effects of bioactive phytochemicals found in whole plant extracts have been related to these positive effects. In this review, we attempted to scrutinize the anti-breast cancer potential of quite a few extracts/ fractions/active components derived from various plant sources such *Alpina galaga, Annona muricata, Ficus carica, Murraya koenigii, Nigella sativa, Rosmarinus officinalis, Urtica dioica,* According to recent research, above mention plants have showed anticancer properties by inhibiting cell proliferation, induces apoptosis and causing cell-cycle arrest in preclinical in vitro and in vivo breast cancer models. This review will help the scientific and medical community for novel drug discovery against breast carcinogenesis.

Keywords: Breast Cancer; Medicinal Plants; Plant Extracts; *Alpinia Galangal; Annona Muricata; Ficus Carica; Murraya Koenigii; Nigella Sativa; Rosmarinus Officinalis; Urtica Dioica*; Phytochemicals

Introduction

Breast cancer is caused by unregulated cell proliferation and differentiation of breast cells. It is the commonest in women and a demanding target for the scientific and medical community [1]. From many centuries, naturally occurring medications have been used to cure various different types of diseases. These medications have always relied heavily on plants, plant extracts, and other plant products. The positive effects of plant extracts/products have been linked to the synergistic impact of phytochemicals present in it. Phytochemicals can impact tumor development processes by modifying and detoxifying carcinogens [2]. The majority of medicinal medications for cancer treatment are also derived

from plants. At present, four classes of plants derived anti-cancer drugs available in the market such as vinca alkaloids, epipodophyllotoxins, taxanes and camptothecin derivatives [3]. Scientists found in the 1960s that an extract from the bark of the Taxus brevifolia could be used to treat cancer [4]. They found that taxol along with vinca alkaloids were very efficient in arresting cell cycle by blocking microtubules depolarization [5]. According to the latest research, some medicinal plant sources such as *Alpina galaga, Annona muricata, Ficus carica, Murraya koenigii, Nigella sativa, Rosmarinus officinalis* and *Urtica dioica* have been effective against breast cancer. In this review, we are principally focused on the most recent research articles of above mention plants. Therefore, the rationale behind this review article is to highlight the protective and beneficial effects of some plant extracts, fractions and active components against breast carcinogenesis which will be helpful for the scientist for novel drug discovery against breast carcinogenesis.

Searching the databases such as PubMed and Google Scholar, yielded information were retrieved by using keywords such as breast cancer+ Alpina galaga, breast cancer+ Annona muricata, breast cancer+ Ficus carica, breast cancer+ *Murraya koenigii*, breast cancer+ *Nigella sativa*, breast cancer+ *Rosmarinus officinalis*, breast cancer+ *Urtica dioica*, plant extract, anti-cancer, phytochemicals etc. Research articles in English language were considered for this review. First, the abstracts of the research articles were reviewed and if relevant, then the complete articles were analyzed for the anti-cancer properties of various plants against breast carcinogenesis.

Protective Effects of Plants on Breast Carcinoma

Alpinia Galanga

Alpinia galanga (AG) belongs to a Zingiberaceae (ginger) family widely distributed in Asian countries. From many centuries, it is used as a spice in food and as herbal medicine for treating various types diseases. Several pharmacological properties of this plant has been discovered by the researchers such as, antioxidant [6,7], anti-inflammatory [8,9] antimicrobial [10], anti-bacterial [11], and anti-osteoarthritic [12]. This plant contains active compounds such as 1'S-1'-acetoxychavicol acetate, 1'-acetoxychavicol acetate, 1'S-1'-acetoxyeugenol acetate, (E)-8, 17-epoxylabd-12-ene-15, 16-dial, p-hydroxycinnamaldehyde, 1, 7-bis (4-hydroxyphenyl)-1, 4, 6-heptatrien-3-one (BH (BDMC). Tumor volume, a major marker of breast cancer, increases in the untreated group of breast cancer, while the tumors in the treated group typically decrease in size as a result of the AG extract. AG also displayed apoptotic and anti angiogenic potential by activating caspase-3 pathway and inhibiting NF-ƙB, NO and COX-2 in breast cancer mice model [13].

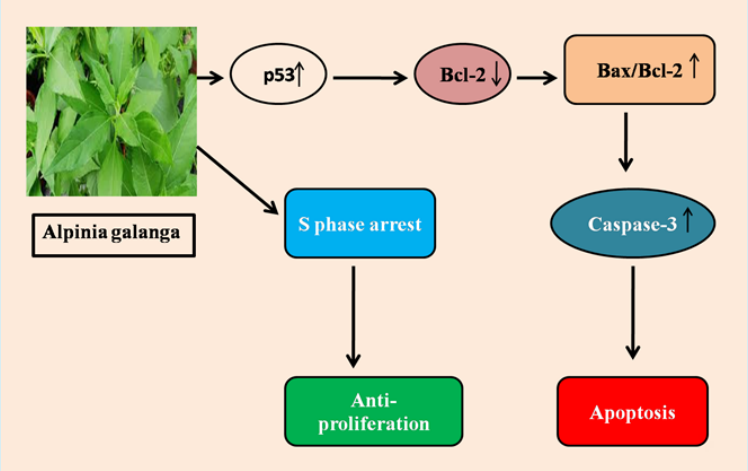

Figure 1: Molecular action of Alpinia galangal: Alpinia galangal stimulates the p53 expression which downregulates the anti-apoptotic Bcl-2 levels followed by upregulation of pro-apoptotic Bax. This upregulation of Bax leads the overexpression of Caspase 3 which finally leading to apoptosis. Additionally, Alpinia galangal also causes S phase arrest in cell cycle and hence acts as an anti- proliferative agent.

Ethanolic extract of AG (96% ethanol) showed cytotoxic effect against MCF7 breast cells lines [14]. According to Song W, et al. [15] galangin, an active component of AG successfully induces apoptosis by TRAIL/Caspase-3/AMPK signalling pathway in human breast cancer cells. AG substantially reduced the proliferation of 4T1 cells at IC50 135 g/mL, and

boosted the cytotoxic effect at concentrations of 50 and 100 g/mL. The quantity of senescent cells arrested in the G2/M phase increased in response to AG. Furthermore, AG reduced 4T1 cell migration and lowered MMP-9 production caused by Dox [16]. Awad MG, et al. [17] discovered a synergistic effect of AG leaves extract and cisplatin against various cell lines viz MCF7, HepG2, CaCo2, and PANC1. This action is mediated via cell cycle arrest, and the decrease of several drug resistance genes (MDR1 and MAPK1). AG also stimulates the p53 expression stimulates apoptosis [18] and causes S phase arrest in cell cycle and hence acts as an anti- proliferative agent [19]. AG was found to enhance the cytotoxic effects of cytotoxic T-cells by restricting the proliferation of human triple-negative breast cancer cells hence displayed immunopotentiation effect [20]. AG has the capability to induce cell senescence and intracellular ROS levels, resulting in delayed cell cycle progression, were linked to its antiproliferation action against HER2-overexpressing breast cancer [21]. 1′-acetoxychavicol acetate component of AG down-regulates the human epidermal growth factor receptor 2, pERK1/2, pAKT, estrogen receptor coactivator, cyclin D1, and MYC proto-oncogene by inhibiting the proliferation of human epidermal growth factor receptor 2-overexpressed cell lines in time and concentration dependent manner.. In addition to this, 1′-acetoxychavicol acetate showed significant reduction in tumor mass in in vivo zebrafish-engrafted breast cancer model [22] (Figure 1).

Annona Muricata

Annona muricata (AM) is an everlasting tropical tree plant belongs to the Annonaceae family. It contains a variety of pharmacological activities like anti-inflammatory [23], anticarcinogenic [24], anti-diabetic [25], antioxidant [26], and anti-microbial [27]. Main phytochemicals present in this plant are annonaceousacetogenins, acetogenins and Cyclohexapeptides [28]. In a breast cancer mouse model, the group treated with AM crude extract had a mean tumor volume of 271.7±14.24 mm, which was smaller than the untreated group's volume of 375 ±25.98 mm. Histological examination revealed the decreased number of mitotic cells per tumor segment upon AM crude extract administration when compared to untreated group. AM crude extract also triggered apoptosis in 4 T1 breast cancer cells, decreased metastasis in vitro and in vivo, regulates the immune system, and reduced cancer-induced inflammation [29]. Ethanolic extract of AM leaves at a dose level of 200mg/kg bw showed significant increase in SOD, MDA, and the histological section of mammary tissue showed lower hyperplasia of mammary epithelial cells [30]. AM leaves extract lowered proliferative indexes of DMBA induced breast cancer, with 300 mg/kg being the most efficacious dose [31]. According to Alshaeri H, et al. [32], Alshaeri HK, et al. [33] AM extract has an anti-proliferative effect via EGFR-mediated signalling pathways such as AKT/MAPK/NF-B pathways and cyclin D1 suppression. Annonacin isolated from Graviola showed marked genotoxicity and inhibitory effect [34] in MCF-7 cells. In breast cancer, ER- functions as a ligand-dependent transcription factor that promotes tumor growth and survival. According to Suhendar U [35] AM extract has the most piperine component, and has cytotoxic action against MCF7 cancer cells which was confirmed by MTT assay. AM extract solid lipid nanoparticles (SLNs) shown a significant apoptotic effect and improved efficacy in killing MCF7 cancer cells [36]. Zeweil MM, et al. [37] reported the downregulation of ER-α gene, increased antioxidants, and reduced lipid peroxidation levels upon Graviola administration. Report by Daddiouaissa D, et al. [38] suggested that the ionic liquid extract of Graviola fruit displayed the anti-proliferative potential on MCF-7 breast cancer cell lines by initiating apoptosis, cell-cycle arrest and by decreasing the cell generation number. AM (ethanol extract) inhibited the proliferation of T47D cell [39], AM (aqueous extract) induces mitochondrial cell death, concealed cell proliferation, and reduced cellular motility in MDA-MB-231 cells [40]. AM leaf (methanol extract) inhibited MCF-7 cells significantly, with an IC50 value of 85.55 g/mL [41]. Another study by Prasad SK, et al. [42] reported that AM seeds extract showed G0/G1 cell cycle arrest via apoptosis. Ethyl acetate extract of AM leaf resulted in a higher level of cytotoxicity on breast cancer cells, which was responsible for anti-proliferative property of extract. In breast cancer cell lines, mitochondrial membrane integrity were significantly down regulated upon AM treatment resulted in the apoptosis of breast cancer cells [43]. The growths of the MCF-7 and MDA-MB-231 cells were inhibited when incubated with AM leaf extracts-loaded scaffolds [44]. Kariyil J, et al. [45] Chloroform fraction of methanolic extract of AM seeds displayed cytotoxicity via cell membrane lysis, ROS dependent caspase-activated mitochondria-mediated apoptosis, and stopping the S phase of the cell cycle. Flowcytometry with propidium iodide staining indicated that AM extract (13 and 25 g/mL) alone caused cell cycle arrest in the G1 phase and G2/M arrest when combined with dox in 4T1 cells. AM extract at doses of 13g/mL and 25 g/mL reduced intracellular reactive oxygen species (ROS) levels as a single therapy and in conjunction with dox, confirmed by dichloro dihydrofluorescein diacetate staining assay [46]. Rojas A, et al. [47] reported the presence of four sesquiterpenes, viz Z-caryophyllene, α-selinene, β-pinene, and β-elemene in the essential oil of AM leaves which is responsible for reduction in MDA and VEGF and elevation in GSH levels in in vivo breast cancer mouse model (Figure 2).

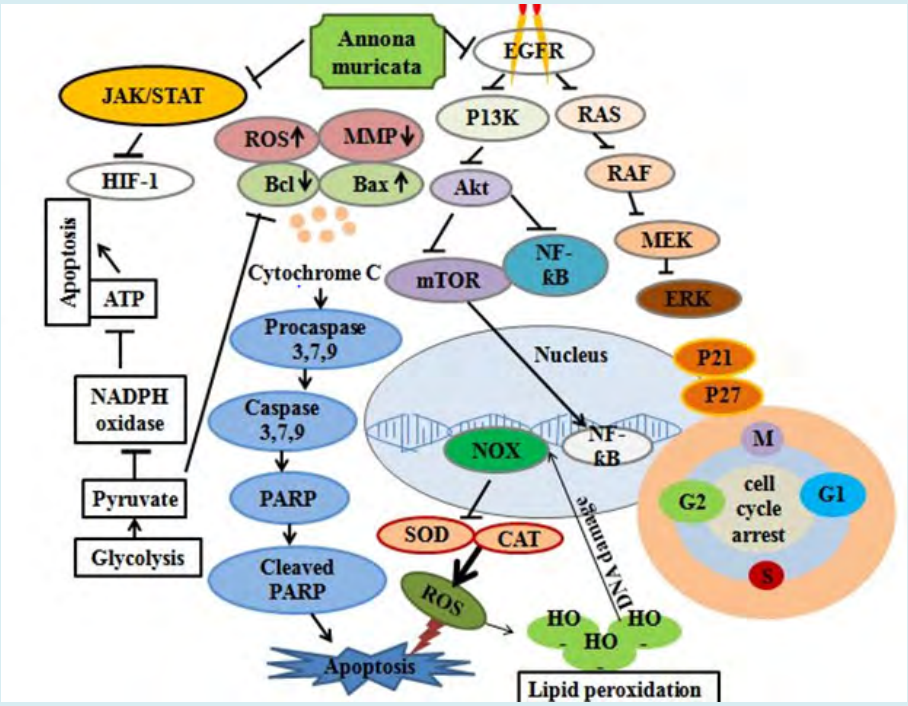

Figure 2: Molecular action of Annona muricata: At a molecular level, AM inhibits the epidermal growth factor receptor (EGFR), which furthers inhibits the other signaling pathways including RAS, phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K), NF-κB, and ERK. AM also inhibits the JAK/STAT pathway which further inhibits the HIF-1α and it also initiates the intrinsic apoptotic pathways by releasing cytochrome c from mitochondria. In addition to this inhibition of enzymes such as superoxide dismutase (SOD), catalase (CAT), and heme-oxygenase (HO-1) increases the production of reactive oxygen species (ROS). These ROS induces the lipid peroxidation and hence DNA damage takes place. All these signaling pathways finally lead to apoptosis, inflammation and cell cycle arrest.

Ficus Carica

Ficus carica (FC) is a flowering plant belongs to family Moraceae, which is formerly from the West Asia and Middle East, but widely distributed in many other regions in the world [48]. The different parts of this plant are used for its medicinal properties in various disorders such as respiratory, inflammatory, cardiovascular and gastrointestinal disorders [48,49] Various pharmacological properties are associated with this plant are antibacterial antioxidant [50,51] anticancer [52,53], Anti-acne [54] and antipyretic [55]. Bioactive compounds in this plant which is responsible for the medicinal properties are arabinose, βamyrins, β-carotines, glycosides, β-setosterols and xanthotoxol Gilaniet al. 2008. Zubair R, et al. [56] reported the high antiproliferative activity and strong cytotoxic activity of ethyl acetate FC extract towards breast cancer (MCF-7) cells line. Aqueous extract of FC leaves decreases the viability of MDA-MB-231 cell, increases the expression level of proapototic gens (BAX) and tumor suppressor genes (TP53, and TP21) showed the anti-prolifertaion activity. Additionally, decreased breast cancer-marker gene (GATA3) and increased proto-oncogene (ELF5) was observed upon FC extract treatment [57]. Ghandehari F, et al. [58] reported that tumor size and volume were both reduced and growth was halted in rats with breast tumors after they were treated with a latex extract of FC. Histopathological evaluation of breast tissue in the fig latex-treated group demonstrated a reduction in angiogenesis, mitotic characteristics, and an increase in necrosis. Another study by Lightbourn AV, et al. [59] suggests that the fig leaf extract attenuates the single-strand breakage upon Diethylstilbestrol-induction in human breast epithelial cells (MCF10A) which was confirmed by comet assay and phase contrast microscopy. FC leaf extract reduces the growth potential of MDA-MB-231 triple-negative breast cancer cells by reducing the S and G2/M cell cycle stages and causing apoptosis via a p53-independent route [60] A study by Widyaningrum N, et al. [61] reported that the fig extract in combination with olive oil showed cytotoxic activity on T-47D and MCF-7 cells and AlGhalban FM, et al. [62] discovered anticancer activity in MDA-MB-231 cells, demonstrating antiproliferative and antimetastatic effects as well as significant effects on cell shape (Figure 3).

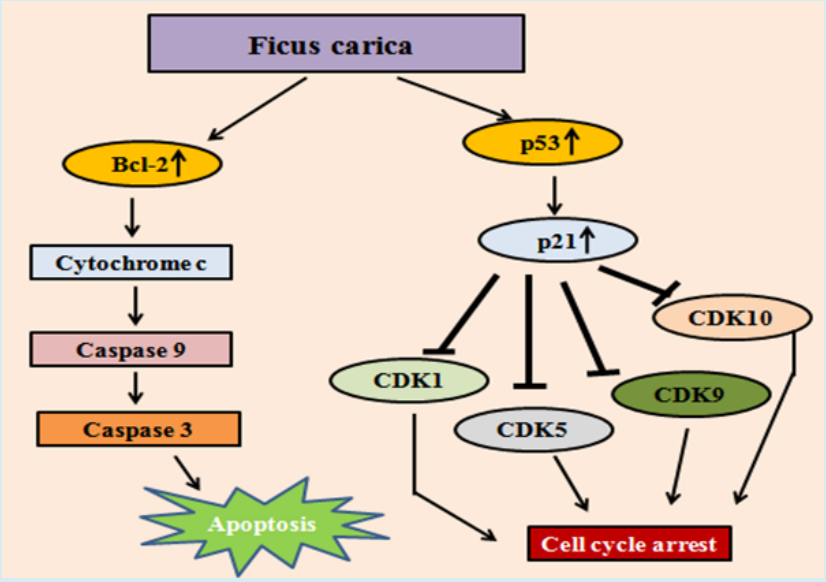

Figure 3: Molecular action of Ficus carica: Ficus carica induced apoptosis via Bax and p53 activation. BAX helps to release cytochrome c from mitochondria followed by activation of caspases leading to cell death. Activation of p53 also activates p21 which furthers inhibits the action of CDKs, hence leads to cell cycle arrest.

Murraya Koenigii

Murraya koenigii (MK), belongs to the Rutaceae family and widely scattered in Eastern-Asia. Various pharmacological properties this plant are antifungal [63], antioxidant [64,65], anti-bacterial [66], antidiabetic [67], anti-inflammatory [68,69] and anticancer [70].

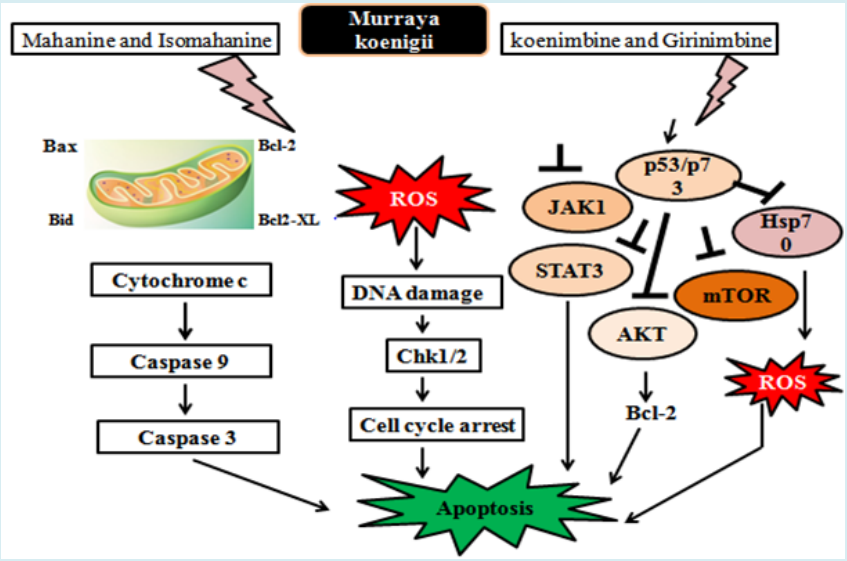

Figure 4: Molecular action on Murraya koenigii: Murraya koenigii and its primary active component regulates multiple signaling pathways, including JAK/STAT, phosphatidylinositol 3 kinase (PI3K)/protein kinase B (AKT) and mammalian target of rapamycin (mTOR). Active constituents viz koenimbine and girinimbine from MK triggered the tumor suppressor gene p53/p73 which in turn inhibits the JAK1, STAT3, mTOR, Hsp90 and AKT. Mahanine and isomahanine from MK responsible for the release of cyctochrome c which furthers initiates cascade of caspases in the intrinsic apoptotic pathway and finally lead to apoptosis. It also triggers the check point of cell cycle and induces the Go/G1 cell cycle arrest.

Various active components of this plants are bismahanine, murrayanine, murrayafoline-A, bi-koeniquinone-A, bismurrayaquinone, mukoenine-A, mukoenine-B, mukoenine-C, murrastifoline, Murrayazolinol, murrayacine, murrayazolidine, murrayazoline, mahanimbine, girinimbine, koenioline, xynthyletin, koenigine-Quinone A and koenigine-Quinone B [71]. Yeap SK, et al. [70] reported that the tumor volume was greatly reduced by MK aqueous extract, and the histological characteristics revealed that MK leaf extract has the ability to manage inflammation, reduction in tumor cells and limit the proliferation of tumor cells. It also reduced nitric oxide levels as well as inflammation-related cytokines and genes such as iNOS, iCAM, NF-kB, and c-MYC, hence stimulates the T cell cytokine production which further helps in reduction of mitotic division and hence delayed the breast cancer formation. MK extract treatment resulted in increased caspase-3 activity and TUNEL-positive cells, indicating accelerated apoptosis [72]. Total alkaloid extract from MK leaves inhibited cell viability (IC50 of 14.4 g/mL), changed growth dynamics, stopped cells in the "S" phase, and promoted cell death of breast cancer cells (MDA-MB-231) [73]. A study by Vijapur LS, et al. [74] revealed the anticancer activity of silver nanoparticles of MK on breast cancer cell lines (MDA-MB-231) by MTT assay. Ethanolic extract of MK showed an anti-cancer activity against DMBA induced breast tumors in rats. Significant decline was observed in tumor mass, quantity of polymorphonuclear leukocytes, multi-layered cuboid epithelium, and proliferated solid collagen fibers upon treatment with MK extract [75]. Additionally Aisyah S, et al. [76] reported the overexpression of caspase-3, linked to apoptosis of cancerous cells and hence showed anti-tumor potency. Apoptotic and anti-angiogenic potential have been displayed by Mahanimbine, an active component of MK against breast cancer cells [77] (Figure 4).

Nigella Sativa

Nigella Sativa (NS), rising as a miracle herb belongs to a Ranunculaceae family. Various pharmacological potential of this herb has been revealed by the researchers such as, anti-inflammatory [78,79], antihypertensive [80], antioxidant [81,82], antidiabetic [83-85], antimicrobial [86,87] and anticancer [88,89]. The chemical component present in this plant are Cumin aldehyde, cuminic alcohol, pyrazines, 2-ethoxy-3-isopropylpyrazine, 2-methoxy-3-sec-butylpyrazine, and 2-methoxy-3-methylpyrazine, terpinene, safranal, p-cymene, pinene, thymoquinone, and monoterpenes. A study by Bhattacharya S, et al. [90] reported that Thymoquinone-Loaded Nanostructured Lipid Carrier displayed the cytotoxicity against Breast Cancer Cell Lines (MDA-MB-231 and MCF-7). Aqueous extract of NS and crude flavonoid extract successfully inhibited the growth of MCF cell lines with the same potency as conventional cisplatin [91,92]. It is also reported that NS aqueous extract consist of elements such as calcium and magnesium etc., and high amount of these elements inside the cell starts the cell death via apoptosis. Histological investigation of NS seed-supplemented DMBA-treated rats demonstrated mammary gland activation and prevention of breast tumor cell proliferation progression. Tumor volume, MDA, LDH levels, as well as ALP and AST activity, were reduced by NS seed oil and Thymoquinone, an active component of NS. TQ was more efficient in lowering Brca1 and Brca2 gene expression [93] and significantly elevates the P53 gene expression [94].

Another study by Periasamy et al. [95] reported of ultrasonic nanoemulsion formulation of NS essential oil induces apoptosis in MCF-7 cell, hence displayed anti-cancer activity. Another Report by Bumidin MS, et al. [96] demonstrated that NS aqueous extracts can reduce the cell membrane integrity of MCF-7 and thereby can restrain the growth and viability of MCF-7. Thymoquinone synchronize the levels of pro and anti-apoptotic genes hence leading to apoptosis. It can impede the process of metastasis via the JNK and p38 activation and lowered the phosphorylation of NF-κB and IKKα/β [97]. Silver nanoparticles (AgNPs) derived from an aqueous seed extract of NS promote apoptosis in MCF-7 cells through changing the expression of apoptotic proteins Bax and Bcl-2, as well as COX-2 (inflammatory marker) [98]. Rafati M, et al. [99] observed that using N. sativa gel as a prophylactic measure effectively delayed and reduced the incidence of ARD and moist desquamation in breast cancer patients. Hydroalcoholic extract of NS showed an inhibitory effect against breast cancer cell lines (MCF 7). Reduction in the mRNA expression levels of NFk and IKK demonstrated the anti-inflammatory effects of NS [100]. Khurshid Y, et al. [101] reported that the proteins isolated from NS have apoptotic and anti- proliferative potential against human breast MCF-7 cancer cell line. In breast cancer, regulation of the PIK3CA kinase domain can be diminished by H1047R and p. H1047L mutants resulting in increased PI3K/Akt1 pathway activation. Unal et al. [102] reported the inhibitory effect of Thymoquinone on proliferation and migration of MDA-MB-231 cells by suppressing autophagy. Zhou J, et al. [103] reported that thymoquinone isolated form NS binds to the kinase domain of PI3CA mutants, preventing TQ-mediated PI3K/Akt1 pathway activation. NS seed oil caused a significant cell proliferation reduction and decreased cell viability and act as anti-carcinogenic, anti-proliferative agent [104,105] (Figure 5).

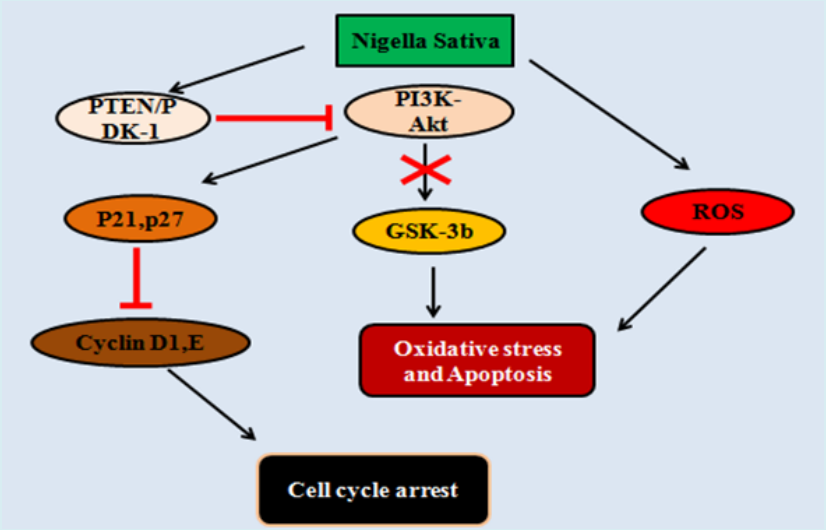

Figure 5: Molecular action on Nigella Sativa: Nigella Sativa suppresses the PI3K-Akt pathways by activating PTEN/PDK-1. After this the inhibition of downstream regulator GSK-3b takes place which further induces the oxidative stress and finally apoptosis. NS also generates the reactive oxygen species which creates oxidative stress condition leading to apoptosis. In addition to this, inhibition of PI3K-Akt activates p21 and p27 which further inhibits the cyclins (D1,E) and leading to cell cycle arrest.

Rosmarinus Officinalis

Rosmarinus officinalis (RO) belongs to Lamiaceae family and widely distributed in the Mediterranean region. RO leaves extract has been used as a flavoring agent [106]. Various pharmacological properties are associated with this plant are anti-oxidant, antibacterial [107,108], anticancer [109] and anti-inflammatory [110,111] antidiabetic [112,113]. The main bioactive compounds present in this plant are rosmarinic acid, caffeoylquinic acids, caffeic acid, quinic acid, kaempferol, rutin, quercetin Mena, et al. A study by Moore J, et al. [114] Showed the increased levels of ADP ribose polymerase (PARP) cleavage which is a well-known markers for apoptosis and essential oil of RO repressed the viability of the MCF-7 cell line at a dose-400 µg/ml concentration (IC50 = 48.01 ± 0.94) [115]. Studies have shown the cytotoxic effects of green iron nanoparticles of aqueous extract of RO [116] and anti-prolifeartive activity of RO extract in combination with bleomycin drug [117] on 4T1 and MCF-7 cell lines. RO suppressed MDA-MB-231 and survival at low concentrations (0.5-20 g/mL) and dramatically lowered the phosphorylation/activation levels of Akt and mTOR, two critical actors in cancer cell growth and survival [118,119]. Shen Y, et al. [120] reported the anti-proliferative property of ethanolic extract of RO against MCF-7 cancer cell lines. RO suppressed MDA-MB-231 and survival at low concentrations (0.5-20 g/mL) and dramatically lowered the phosphorylation/activation levels of Akt and mTOR, two critical actors in cancer cell growth and survival [121] (Figure 6).

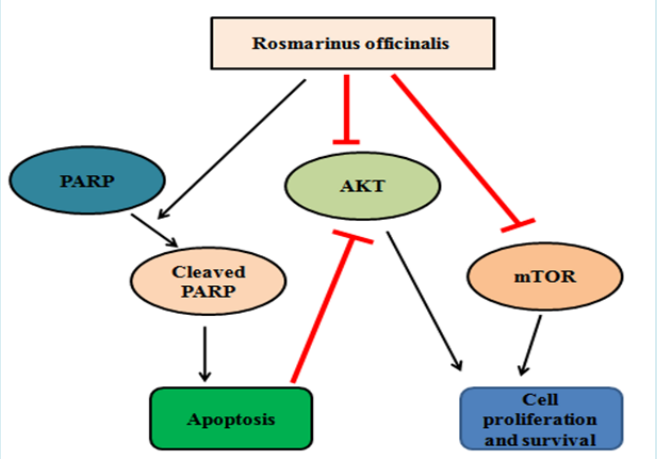

Figure 6: Molecular action of *Rosmarinus officinalis: Rosmarinus officinalis* increases the levels of cleaved Poly (ADP-ribose) Polymerase (PARP) which is a main apoptotic marker. Additionaly, it also downregulates the activation and phosphorylation process of AKT and mTOR which are the key players for controlling cancer cell proliferation.

Urtica Dioica

Urtica dioica (UD) is an herbaceous perennial flowering plant, belongs to family Urticaceae and genus

Urtica, widely distributed in distinct parts of the world like India, United States, Malaysia, and Iran [122]. Number of pharmacological properties are associated with this plant are anti-inflammatory [123], anticancer [124], antirheumatic [125] and cardiovascular [126], antiaging and antioxidant [127]. Bioactive components present in this plant are mainly flavanoids such as kaempferol, isorhamnetin, quercetin, isoquercitrin, astragalin, rutin, 3-rutinosides and 3-glycosides [128]. A study by Mohammadi A, et al. [129] reported the apoptotic potential of the UD plant extracts against MDA-MB-468 breast cancer cell lines. Later on, another study by Mohammadi A, et al. [130] suggests the cytotoxic activity of UD dichloromethane extract on growth and migration of MDA-MB-468 cells assessed by TUNEL assay and DNA fragmentation analysis. Real-time polymerase chain reaction (PCR) has revealed the increased mRNA expression levels of caspase-3, caspase-9, and decrease in the bcl-2 showed the mechanism of cell death. A study by Telo S, et al. [131] reported the reduced lipid peroxidation and elevation in catalase enzyme activity in rat mammary gland cancer. Histological investigation revealed that animals in the malignant group that were treated with UD had a moderate degree of ductular proliferation along with localised epithelial hyperplasia. A research by UD extract has the ability to regulate miR-21 and its associated gene in breast cancer, as well as limit the development and migration of breast cancer cell lines and in vivo models [132]. Mohammadi A, et al. [133] reported the anti-cancer efficacy of UD extract (dichloromethane solvent) on in vitro 4T1 breast cancer cell line and in vivo mouse 4T1 allograft tumor model. Authors have revealed the cytotoxic potency of UC extract on 4T1 breast cancer cell line and 4T1- induced mouse model by MTT assay. Addtionally, UC treatment induces the apoptosis in 4T1 cells and Balb/c allograft tumor model, confirmed by DNA fragmentation and TUNEL (terminal deoxy transferase (TdT)-mediated dUTP nick- end labeling) assay respectively. Further, growth of breast tumor was also reduced upon treatment with UC extract. Real-Time PCR exhibited the upregualtion of proapoptotic caspase 3 and caspase 9 whereas downregulation of anti-apoptic Bcl-2. Akbarian et al. [134] reported that cytotoxic effects of zinc oxide nanoparticles on MCF-7 and Fattahi S, et al. [135] demonstrated the anti-cancer effect of UD aqueous extract on MCF-7, MDA-MB-231 cell lines by evaluating adenosine deaminize (ADA) and ornithine decarboxylase (ODC1) gene expression. They observed that the UC induces apoptosis in breast cancer cells by increasing the expression of ODC1 in both cell lines and upregulating the expression of ADA in MCF-7 cell lines. Hydroalcoholic extract of UD at 1200 µg/ml inhibits the proliferation of MCF-7 breast cancer cells [136] (Figure 7) Table 1.

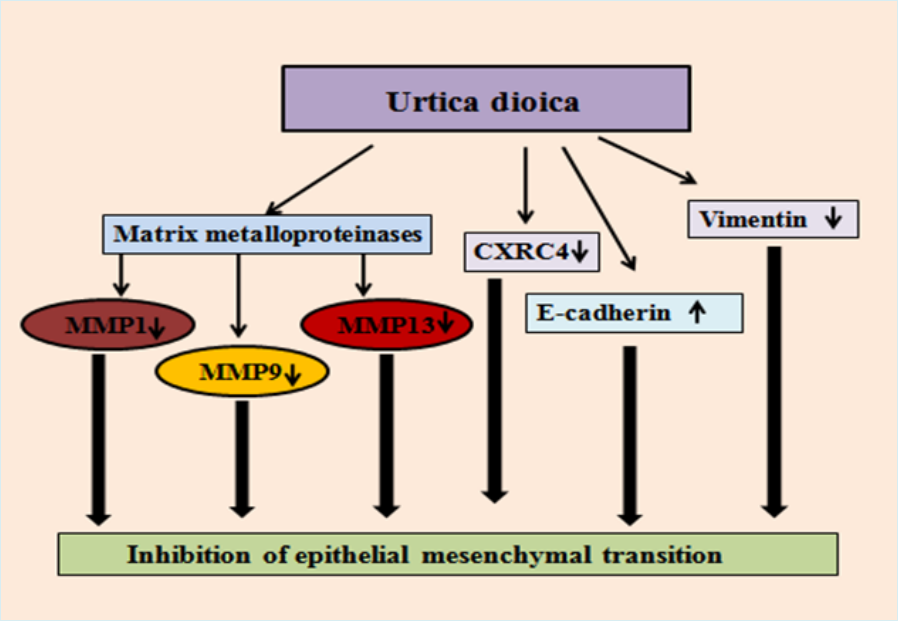

Figure 7: Molecular action of Urtica dioica: Urtica dioica suppresses metastasis-related genes in breast cancer by regulating the miR-21, MMP1, MMP9, MMP13, vimentin, CXCR4, and E-Cadherin Mansoori B, et al. [133].

Plant extract/fraction	Experimental model	Anti-cancer effect	Reference
Alpinia Galanga			
Rhizome extract	MCF-7 cancer cells	Cytotoxic effect	[13]
	HER-2 over expressing breast cancer cells	Senescence effect, Apoptotic effect	[21]
Root extract	Breast cancer mice model	Anti-proliferative property	[14]
	4T1- cancer cells	Cytotoxic effect, Senescence effect, Apoptotic effect, Anti-metastatic	[16,18]
	MDA-MB-231 cancer cells	Immunopotentiation effect	[20]
Leaves extract	MCF-7 cancer cells	Cytotoxic effect, Apoptotic effect	[17]
Nanoparticles (Rhizome extract)	MDA-MB-231 cancer cells	Anti-proliferative property	[19]
Acetoxychavicol acetate (isolated from Alpinia galangal)	MCF-7, HER-2, Zebrafish xenograft model	Anti-tumor effect	[22]
Galangin (isolated from Alpinia galangal)	MCF-7 cancer cells, Mice bearing MCF-7 tumor xenografts	Anti-metastatic, Apoptotic effect	[15]
Annona Muricata			
Leaves extract	Breast cancer model (in-vivo)	Inhibits carcinogenesisis	[29]
	Rat breast cancer model	Anti-proliferative property	[31]
	MCF-7 cancer cells	Cytotoxic effect, Anti-proliferative, Apoptotic effect, Genotoxic	[30,34,35,40,41,43,44]
	MDA-MB-231 cancer cells	Cytotoxic, Suppress cell proliferation, Decreased cell motility	[30,40,44]
	4T1- cancer cells	Cytotoxic effect	[30]
	Triple negative breast cancer (TNBC) cells	Anti-proliferative effect	[32,33]
	T47D breast cancer cell lines	Cytotoxic effect	[39]
Fruit extract	Rat breast cancer model	Apoptotic effect, Antioxidant effect	[37]
	MCF-7 cancer cells	Anti-proliferative, Anti-inflammatory, Cytotoxic, Apoptotic effect	[38]
	MDA-MB-231 cancer cells	Apoptotic effect	[42]
Pulp extract	MCF-7 cancer cell	Genotoxic effect	[41]
Seed extract	MCF-7 cancer cells, MDA-MB-231 cancer cells, Triple negative breast cancer (TNBC) cells, 4T1- cancer cells	Apoptotic effect, Antioxidant effect Cell-cycle arrest	[42,45]
Nanoparticles (fruit extract)	MCF-7 cancer cells	Apoptotic effect	[6]
Ficus Carica			
Leaves extract	MDA-MB-231 cancer cells	Anti-proliferative, Anti-metastatic, Cell-cycle arrest, Apoptotic effect	[57,59]

Leaves latex	Rat breast cancer model	Antioxidant effect, Apoptotic effect, Anti-inflammatory	[58]
	MDA-MB-231 cancer cells	Anti-proliferative, Anti-metastatic	[62]
Fruit extract	MCF-7 cancer cells, T47D cancer cells, 4T1- cancer cells	Anti-proliferative, Cytotoxic effect	[56,61]
Murraya koenigii			
Leaves extract	MDA-MB-231 cancer cells	Cytotoxic effect	[70]
	In vivo breast cancer model	Immunomodulatory, Anti-inflammatory, Apoptotic effect	[70,72,75,76]
Leaves Alkaloids extract	MDA-MB-231 cancer cells	Apoptotic, Cell cycle arrest	[73]
Silver nanoparticles (Leaves extract)	MDA-MB-231 cancer cells	Cytotoxic effect, Apoptotic effect	[74]
Nigella Sativa			
Seed extract	MCF-7 cancer cells	Anti-neoplastic, Cytotoxic, Anti-proliferative	[91,100,101]
Seed oil	MCF-7 cancer cells	Cytotoxic, Anti-inflammatory, Reduced cell-viability	[95,105]
Silver nanoparticles (Seed extract)	MCF-7 cancer cells	Cytotoxic, apoptotic Anti-inflammatory	[98]
Thymoquinone (isolated from Nigella sativa)	MCF-7 cancer cells	Cytotoxic	[90]
	MDA-MB-231 cancer cells	Suppress autophagy, anti-neoplastic	[102,104]
	In-vivo breast cancer model	Anti-migratory, Apoptotic, Anti-oxidant effect	[90,93]
Rosmarinus Officinalis			
Leaves extract	MDA-MB-231 cancer cells	Anti-proliferative, Apoptotic, Reduced survival	[119]
Leaves oil	MCF-7 cancer cells	Cytotoxic	[115]
Aerial part extract (stem, fruit, leaf)	MCF-7 cancer cells	Cytotoxic, Anti-proliferative	[117]
Phenolic extract (leaves)	MCF-7 cancer cells	Anti-proliferative, Apoptotic	[120]
Iron nanoparticles (Leaves extract)	4T1- cancer cells	Cytotoxic	[116]
Rosmarinic acid (from *Rosmarinus officinalis)*	In vivo breast cancer model	Anti-inflammatory, Anti-angiogenic, Apoptotic	[121]
Urtica Dioica			
Leaves extract	MCF-7 cancer cells, MDA-MB-231 cancer cells 4T1- cancer cells	Anti-metastatic, Growth inhibition, Suppress miR-21	[130]
Urtica dioica extract (stem leaves, roots)	MDA-MB-468 cancer cells	Cytotoxic, Cell-cycle arrest	[128,129]
	In-vivo breast cancer model	Anti-metastatic, Antioxidant effect	[131]

Table 1: Anti-cancer effects of Plant extracts/ fractions/ phytochemicals/in breast cancer.

Conclusion and Future Perspectives

Prevention can be a good and cost effective strategy for a dreadful disease like cancer. Daily intake of herbs in infusions or in meals could be an advantageous for consumers as it may protects tissue against oxidative stress hence preventing the initiation of cancer. According to recent research, *Alpina galaga, Annona muricata, Ficus carica, Murraya Koenigii, Nigella sativa, Rosmarinus officinalis*, and *Urtica dioica* have shown anticancer properties by inhibiting tumor volume,

cell proliferation, improving histoarchitecture, inducing apotosis, and causing cell-cycle arrest in preclinical in vitro and in vivo breast cancer models. However, it is necessary to investigate the effects of these plants on humans through clinical trials in order to bring new products to the market either as a chemopreventive medicine or as an anticancer drug.

Declaration of Competing Interest

Authors declare no conflict of interest.

Authors Contribution

Shilpa Sadwal: literature survey, writing the manuscript; Sarvnarinder Kaur: review and editing the manuscript; Aniqa Aniqa: literature survey, editing the manuscript. The final manuscript was read and approved by all of the authors.

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