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The use of medicinal plants for combating breast cancer: A comprehensive review

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ABSTRACT

Breast carcinoma is a common illness among females. Various therapies, including hormone therapy, surgery, radiotherapy, chemotherapy, and targeted treatment, have been available to treat existing breast cancer. These therapies can potentially halt the development and spread of cancer, especially if the disease is at an early stage, but all these treatments have various adverse effects on human health. Cancer cells proliferate more rapidly than most normal cells, so chemotherapy is the most suitable treatment. Certain medications can cease dividing cells by destroying the cell's control center region. Other drugs can inhibit the chemical processes essential for cell division. On the contrary, because cancer is frequently identified at a late phase, treating the disease is extraordinarily challenging. Therefore, it is advisable to avoid this fatal condition from occurring. Multiple studies have revealed a continuous inverse connection between cancer and natural materials, such as plant extracts, their fractions, and active principles. These bioactive phytochemicals' have synergistic or cumulative effects in the treatment of cancer disease. This review article examined the effect of various extracts/fractions/active principles obtained from diverse plant origins against breast cancer disease. Information regarding the most commonly used plants, including *Alpina galaga*, *Urtica dioica*, *Annona muricata*, *Rosmarinus officinalis*, *Ficus carica*, *Nigella sativa*, *Murraya koenigii*, and *Urtica dioica* have been presented in this study. Owing to the information in this study, these plants exhibited anticancer activities in preclinical MCF-7 carcinoma models by decreasing cell proliferation, inducing programmed cell death, and triggering cell-cycle arrest. The information generated from this review will significantly contribute to developing knowledge of the scientific and medical communities in developing innovative breast cancer treatments.

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1 Introduction

Random proliferation and differentiation of breast cells are the cause of breast cancer. It is common among females and reported as an important medical problem (Saha et al. 2021). Several factors including family history, the existence of BRCA1 or BRCA2 genes, pregnancy after age 30 or infertility, lack of physical exercise, being overweight or obese, and having dense breast tissue, are responsible for developing breast cancer. Along with these, increased usages of alcohol, oral contraceptives, and hormone replacement treatment (HRT) containing just estrogen may also be responsible for the development of breast cancer (Dhama et al. 2018; Abd El-Hack et al. 2022; Rafeeq et al. 2023). Other factors include cigarette smoking, exposure to chemicals like digoxin, ethylene oxide, polychlorinated biphenyls, a prior history of breast cancer (Figure 1), and previous treatment with radiation, particularly before the age of 30, are also associated with the development of cancer.

Over many years, numerous illnesses have been treated with naturally occurring medications. Historically, these treatments depend on herbs, plant extracts, and other plant-based compounds. The advantages of these treatments are the synergistic effect of phytochemicals and other plant-based products without any side effects. Previous studies have already well established the role of various phytochemicals in cancer treatment; these plant products may affect cancer development by altering and detoxifying carcinogens (Abdel-Basset et al. 2020). The four most common anticancer drugs with plant derivatives are vinca alkaloids, epipodophyllotoxins, taxanes, and camptothecin (Upreti et al. 2022). In the 1960s, researchers discovered the role of *Taxus brevifolia* bark extract in cancer treatment (Wani et al. 1971). Taxol and vinca alkaloids were also found effective in stopping the cell cycle by preventing the depolarization of microtubules (Zajączkowska et al. 2019). Recent review article have comprehensive information on some selected plant sources, including *Annona muricata*, *Nigella sativa*, *Ficus carica*, *Alpina galaga*, *Murraya koenigii*, *Urtica dioica*, and *Rosmarinus officinalis*, and their role in the treatment of breast cancer (Dhama et al. 2018; Abd El-Hack et al. 2022; Rafeeq et al. 2023). This study emphasizes the protective and therapeutic impacts of various herbal extracts, fractions, and bioactive constituents on treating breast cancer.

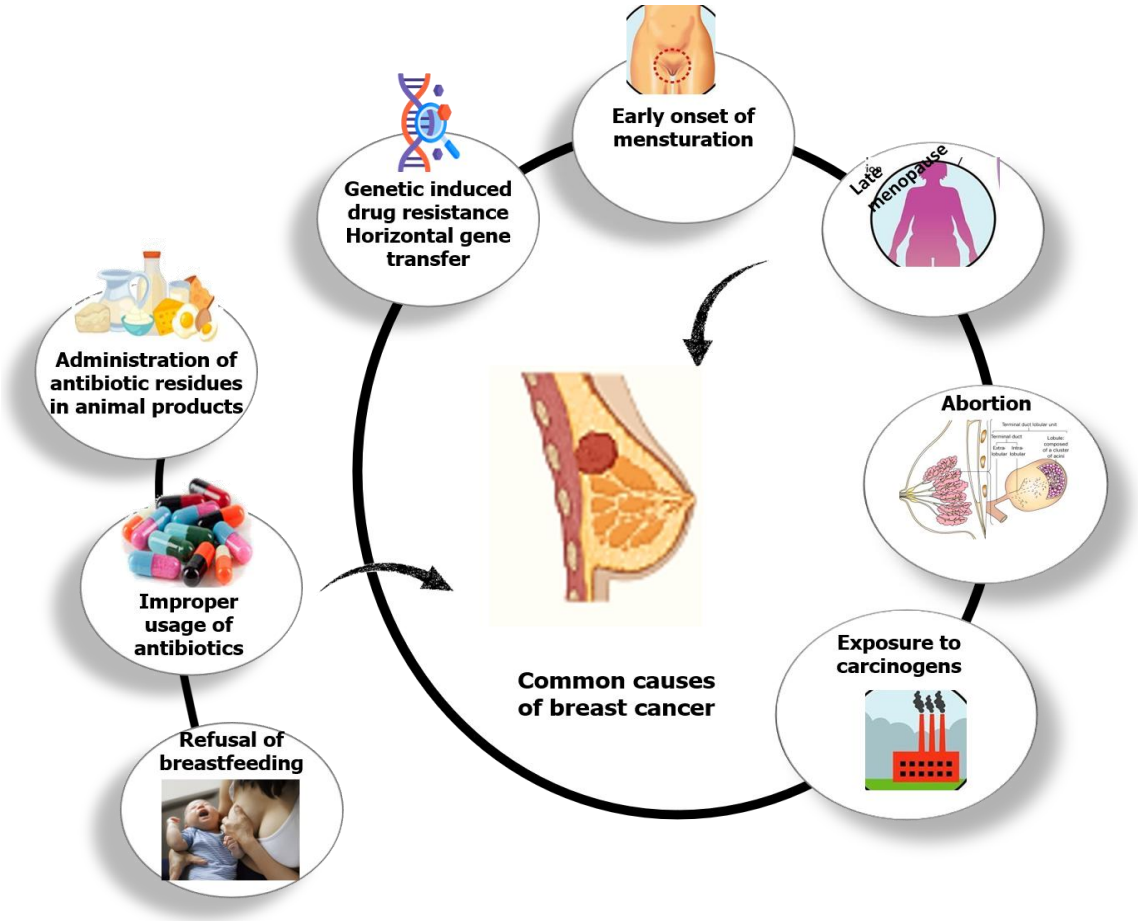

Figure 1 Common causes of breast cancer

2 Classification of various cancers

Cancer is a severe form of the disease that is characterized by uncontrolled cell development. The growth, differentiation, and death of body cells are generally well-programmed. In contrast, some cells, especially those bearing somatic and epigenetic mutations, may escape destiny and grow out of control (Alshaeri et al. 2018; Alshaeri et al. 2020). This kind of abnormal growth can form the so-called neoplasm. A localized neoplasm restricted to the tissue of origin is a benign tumor, while neoplasms can invade other tissues and form secondary tumors, malignant tumors, namely cancer (Alshaeri et al. 2018; Alshaeri et al. 2020). Cancer is also caused by a succession of gene changes that alter the cell's functions (Hassanpour and Dehghani 2017). There are around 100 different forms of cancer that have been identified. The origin and kind of cell are the most critical factors in classifying malignancies (Hiatt et al. 1977). Cancer invades the body's immune system by controlling the body cells in a way that leads to lumps and masses of tissue, otherwise called abscesses. Owing to annual studies, cancer is responsible for over 2% of fatalities worldwide.

Furthermore, according to the American Cancer Society (ACS), 14.1 million people were newly diagnosed with cancer cases in 2012, of which 8.2 million died. It is expected that around 21.7 million people will be diagnosed with tumors by 2030, among these 13 million being in their terminal stage of cancer (Edge et al. 2010). Many lifestyle difficulties, including smoking, physical inactivity, poor diet, and low pregnancies, contribute to cancer risks, particularly in the American cancer community's developing countries (Srivastava and Tiwari. 2022).

Somatic mutations in oncogenic and tumor suppressor genes may ultimately lead to cancer development. In the case of human beings, cancer can begin almost anywhere in the human body. In the case of man, lung, prostate, bronchus, colon, rectum, and urinary bladder cancer is the most common type. While in the case of females, breast, lung, bronchus, colon, rectum, uterine corpus, and thyroid cancer are common. Owing to this data, prostate and breast cancer account for a significant part of the tumor in males and females, respectively. Blood cancer and malignancies of the brain and lymph nodes are responsible for the highest percentage of cancer patients among youngsters. The top six cancer types for both sexes account for more than 50% of newly detected cancer patients and deaths worldwide. Breast cancer in females is the most estimated tumor type (11.7% of total cases) in 2020, subsequent by lung (11.4%), prostate (7.3%), colorectal (10.0%), gastric (5.6%), and liver (4.7%) cancers (Prasad et al. 2020). The most estimated cancer mortality came from lung cancer (18%), subsequent colorectal (9.4%), stomach (7.7%), liver (8.3), and breast (6.9%) cancers. For males, prostate cancer is responsible for 32.5% of estimated new cancer patients in 2020, followed by colorectum (10.5%), bladder (6.6%), lung (6.4%) cancers, and melanoma of the skin (6.4%) (Naik and Sellappan 2021). For females, breast cancer currently accounts for 26.2% of estimated new cancer cases in 2020, followed by colorectum cancer (11.2%), lung cancer (8.4%), melanoma of the skin (7.4%), and corpus uteri cancer (5.1%). Cancer-related mortality is variable in different cancer types. The most significant cancer mortalities in Sweden are expected from lung cancer (15.7%), colorectum cancer (12.7%), prostate cancer (9.8%), and pancreatic cancer (8.3%) (Prasad et al. 2020; Kariyil et al. 2021). The major types of cancer can be classified into five border groups as follows

1 Carcinoma is cancer that affects cells within and outside the body, including the mammary gland, lungs, and intestine colon.
2 Sarcoma can be identified by the location of cells in the body, such as bones, adipose tissue, muscles, etc.
3 Lymphoma is a malignancy affecting lymph nodes and other immune system organs.
4 Leukemia is a bone marrow malignancy that frequently manifests in the blood.
5 Adenomas originate in secretary glands, such as the thyroid, adrenal, pituitary, and other thyroid tissues (Dhama et al. 2018; Abd El-Hack et al. 2022; Rafeeq et al. 2023).

3 Medicinal plants as anticancer agents

Herbs have a long history of being used in cancer therapy. In the analysis of cancer-fighting plants, Hartwell included over 3000 plants that can be used in cancer treatment (Arain et al. 2022; Abd El-Hack et al. 2022). The Greek physician Hippocrates (460-370 BC), known as the "Father of Medicine," created the term "cancer." Abscesses and ulcers were referred to as "carcinoma" by Hippocrates. Another Roman physician, Galen (130-200 AD), used the term once (a Greek word meaning swelling) to denote tumors (Zishan et al. 2017). Cancer is the world's 2nd largest etiology of death. Cancer was becoming more common in 2014, and around 1,665,540 people in the United States had cancer, with 585,720 dying (Zishan et al. 2017).

Surgery, chemotherapy, and radiotherapy are most commonly used in cancer treatment but are effective only in the condition of early diagnosis (Agarwal et al. 2013). Instead of these therapies, medicinal plants can provide raw materials and high-quality food for livelihoods which can fight against illnesses. Based on traditional applications and scientific data, much study has been done on these herbs for tumor treatment, and several plant products have been commercialized as anticancer medications (Chanchal et al. 2018). Medicinal plants are estimated to have over 8,000 species, and some of these plants have been effectively used for medicinal purpose; their significance is also scientifically established, while traditional healer still utilizes others, but their scientific medicinal value has yet to be discovered. Western uses of these data are now being scrutinized more closely, and most

academic and industrial researchers now respect national and indigenous rights to these resources (Chanchal et al. 2018). Approximately three-quarters of the world's population use plants and other traditional medicine to treat ailments. There are at least 250,000 different plant species, with over a thousand having anti-cancer properties (Chanchal et al. 2018).

Medicinal herbs continue to have a significant part in the healthcare system of the world (Abd El-Hack et al. 2019, 2022). Plants' medical and economic advantages are being more widely recognized and developed in emerging nations and enterprises. Herbal supplements, botanicals, and phytomedicines are the products of botanicals used to cure or improve an individual's health. In herbal treatments, raw herbal medications were used to cure illness problems, typically incurable, or to reach or maintain a better state of health were used in medical treatment for an extended period (Chanchal et al. 2018). Because of natural antioxidants, plant-based herbal products serve as decreasing agents and natural remedies that can combat cancer. Bioactive compounds, like isoflavones, flavones, flavonoids, coumarins, anthocyanins, catechins, lignans, and iso-catechins, account for a significant portion of their antioxidant activity, and these natural products can mitigate or reduce the toxic side effects of radiation and chemotherapy by strengthening their anti-cancer action (Nema et al. 2013).

4 Cytotoxicity of some medicinal plants against breast cancer

The study of cancer treatment has expanded significantly. Both traditional and highly contemporary methods are used for the treatment of cancer. Chemotherapy, radiation therapy, and surgery are some standard methods widely used to treat cancer, but each has certain drawbacks. Alternative therapeutic options are required due to the increased cancer incidence worldwide, and herbal therapy offers a convenient alternative to conventional cancer treatment (Yeap et al. 2015).

After going through the previously published literature, some plants were shortlisted which have significant effects against many cancers cell lines, including those found in the breast, gastric, colon, oral, lung, liver, cervical, and blood systems. This review article chose plants based on their reported solid anticancer properties. The presence of secondary metabolites in the plant extracts has shown anti-cancerous properties by inhibiting cancer cell lines via DNA destruction or activating enzymes inducing apoptosis. Herbal medicines are a safe, non-toxic, and widely accessible source of cancer-fighting rather than chemical therapeutics. Because of their various features, medicinal plants are thought to neutralize the impacts of diseases on the body and improve body performance (Aisyah et al. 2020).

Phaleria macrocarpa and *Fagonia indica* have historically been used as anticancer drugs. Active compounds such as gallic acid derived from the abovementioned plant cause apoptosis in cancer cells. Gallic acid was isolated as an active ingredient from *P. macrocarpa's* fruit extract and has been shown to cause apoptosis in lung cancer, leukemia, and colon adenocarcinoma cell lines (Aisyah et al. 2021). Figure 2 has shown the antitumor potential of some selected medicinal plants against breast cancer cell lines. A brief description of these plants have been given in the next section of this review article.

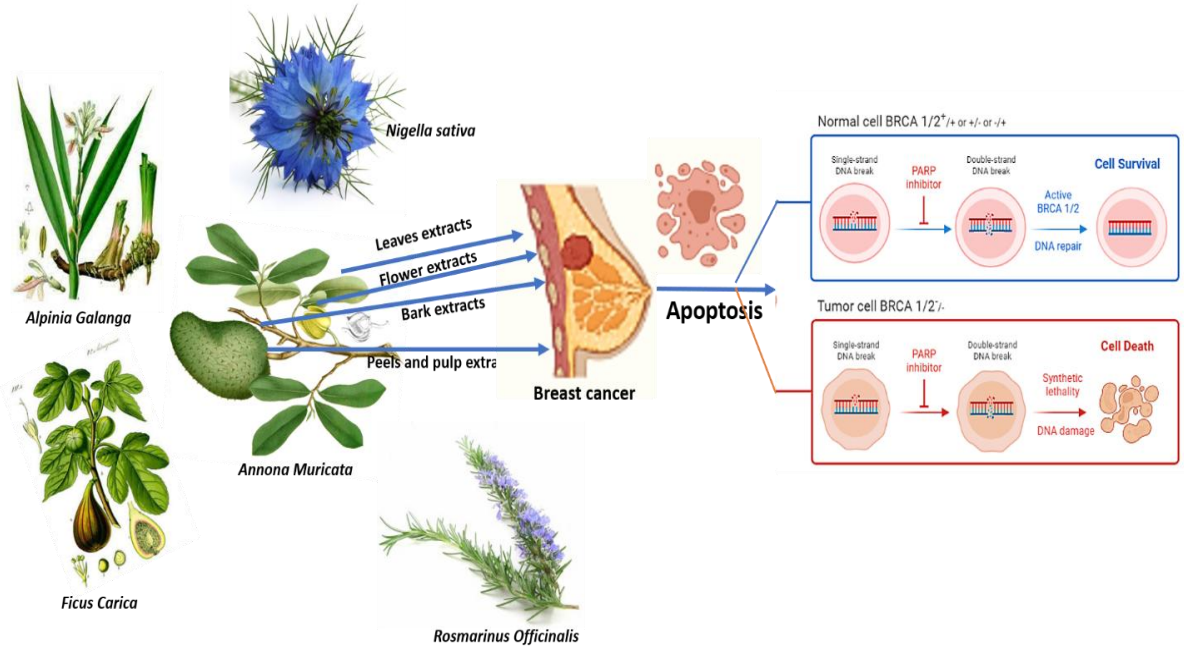

Figure 2 The antitumor potential of some medicinal plants against breast cancer, following examples of some medicinal plants.

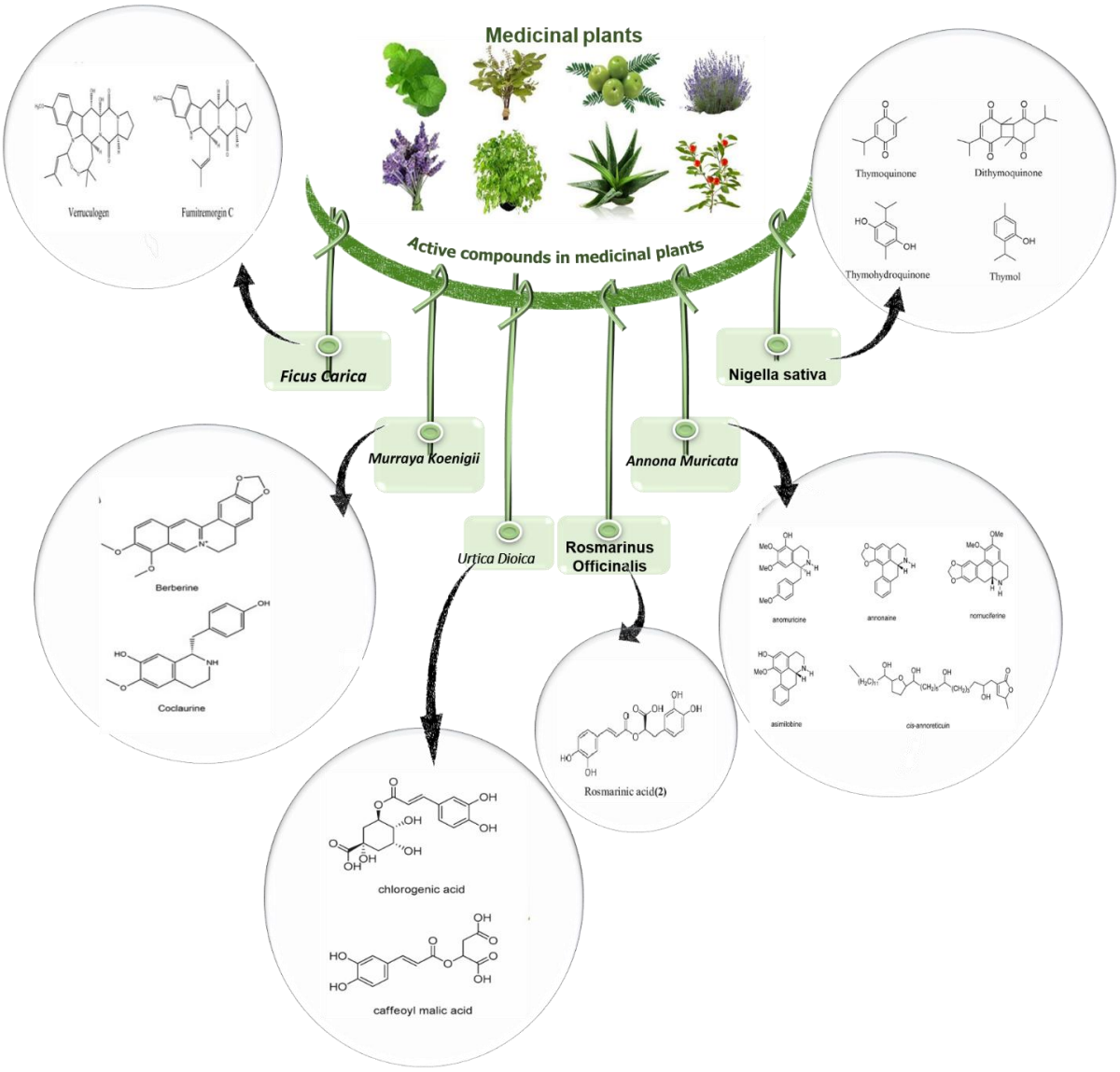

Figure 3 Active compounds in medicinal plants.

4.1 *Annona muricata*

Annona muricata (AM) is a tropical evergreen tree belonging to the family Annonaceae. Its pharmacological characteristics of this plants are associated with various activities like anti-inflammatory (Oliveira et al. 2017), anti-cancerous (Paul et al. 2013), antidiabetic (Spector et al. 2006), antioxidant (Spector et al. 2006), and antimicrobial activities (Pai et al. 2016). The plant contains mostly annonaceous acetogenins, acetogenins, and Cyclohexapeptides active ingredients (Figure 3) (Gajalakshmi et al. 2012). In a mouse model of breast cancer, the group treated with *A. muricata* raw extract had a smaller tumor size than the group that received no treatment (271.714.24 mm vs. 37525.98 mm). Histological analysis of tumor tissue revealed that treatment with *A. muricata* crude extract diminished the number of mitotic cells per tumor segment contrasted to the control group. In addition, *A. muricata* crude extract promoted programmed cell death in 4 T1 breast tumor tissues, reduced metastasis in most studies, regulated immunity, and lowered cancer-related inflammation (Syed et al. 2016). Ethanol extract of *A. muricata* leaves at a dose of 200 mg/kg bw enhanced MDA, SOD, and the histological portion of breast cells demonstrated a reduction in mammary epithelial hyperplasia (Muchtaromah et al. 2015). The highest efficacious dose of *A. muricata* leaf extract against DMBA-induced breast cancer development was 300 mg/kg (Sulistyoningrum et al. 2017). Further, Alshaeri et al. (2018, 2020) also reported that *A. muricata* extract suppresses proliferation by inhibiting EGFR-mediated signaling pathways, including

AKT/MAPK/NF-B and cyclin D1. Similarly, genotoxic annonacin isolated from *A. muricata* inhibited the growth of MCF-7 cells. ER actions as a ligand-dependent gene transcription enhance cancer progression in breast cancer. Due to its high piperine concentration, the MTT assay indicated that *A. muricata* extracts significantly affected MCF7 cancer cells. Similarly, Gudykunst and Nishida (1984) reported that solid lipid nanoparticles (SLNs) produced from *A. muricata* extract have a significant apoptotic impact against the MCF7 cancer cell line. Zeweil et al. (2019) suggested that treatment with *A. muricata* down-regulates the ER gene increases antioxidant characteristics and reduces lipid peroxidation. Also, Daddiouaissa et al. (2019) found that *A. muricata* fruit ionic liquid extract displayed an anti-proliferative effect on MCF-7 breast tumor cell lines by inducing apoptosis, arresting the cell cycle and lowering the number of new cells generated. Ethanolic extract of *A. muricata* inhibits T47D cell proliferation (Fertilita et al. 2020), stimulates mitochondrial cell death, inhibits cell growth, & reduces cellular motility in MDA cells (Kim et al. 2018). The IC50 value of the methanolic extract of *A. muricata* leaves was 85.55 g/mL against the MCF-7 cell line (Naik and Sellappan 2021). In another Prasad et al. (2020) research, *A. muricata* seed extract also induced apoptosis-mediated G0/G1 cell cycle arrest. In MCF-7 cell lines, *A. muricata* treatment significantly weakened the integrity of mitochondrial membranes, resulting in the death of breast cancer cells. The anti-proliferative effect of the ethyl acetate extract of AM leaf was due to a larger quantity of cytotoxicity on breast tumor tissue, which was caused by the *A. muricata* extract (Hadisaputri et al. 2021). Incubation of MCF-7 and MDA-MB-231 cells with scaffolds, including *A. muricata* leaf extract, inhibited their growth (Akpan et al. 2021). Kariyil et al. (2021) also demonstrated the lethal effect of *A. muricata* seeds extract by cellular membranes lysis and S-stage arrest. Similarly, Salsabila et al. (2021) suggested that 13 and 25 g/mL of *A. muricata* extract induced apoptosis in the G1 phase and G2/M arrest in 4T1 cells when paired with DOX by decreasing intracellular reactive oxygen species (ROS) levels. The essential oil of *A. muricata* leaves four sesquiterpenes, i.e., Z-caryophyllene, selinene, pinene, and elements, which are responsible for a decrease in MDA, VEGF levels & a rise in GSH degrees in a mouse model (Rojas-Armas et al. 2022; Figure 2).

4.2 *Alpinia galanga*

Alpinia galangal (AG) is a member of the Zingiberaceae family and is commonly found on Asian continents. It has been widely used as a culinary spice and herbal medicine to cure different illnesses for many years. Many pharmacological properties including antioxidant (Malik et al. 2016; Tang et al. 2018), anti-inflammatory (Baldo et al. 2016; Subash et al. 1970), antimicrobial (Saptiani et al. 2016), antibacterial (Hamad et al. 2016), and antiosteoarthritic activities (Chouni and Paul 2018) have been associated with this plant. This plant contains 1, 7-bis (4-hydroxyphenyl)-1, 4, 6-heparin-3-one (BH), 1,′S-1′-acetoxyeugenol acetate, and (E)-8, 17-epoxylab-12-ene-15 (BDMC) (Figure 3). In a mouse model of breast cancer, *A. galangal* extract exhibited apoptotic & anti-angiogenic effects by stimulating the caspase-3 pathway & preventing the NF-kB, NO, & COX-2 ways (Asri and Winarko 2016). The ethanolic extract of *A. galangal* was cytotoxic to MCF7 breast cell lines (Suhendi et al. 2017). Owing to Song et al. (2017), in human breast tumor cells, the active compound of *A. galangal*, i.e., galangin, inhibits the signaling cycle of TRAIL/Caspase-3/AMPK. *A. galangal* substantially reduced the development of 4T1 cells at IC50 concentrations of 135 µg/mL, whereas the cytotoxic impact increased at 50 and 100 µg/mL. In addition, *A. galangal* inhibited 4T1 cell migration & Dox-induced MMP-9 production. Leaves extract, and cisplatin demonstrated a synergistic impact on various cell lines involving MCF7, HepG4, CaCo2, & PANC1(Ahlina et al. 2020; Awad et al. 2020). This effect is achieved by stimulating apoptosis and lowering drug resistance genes (MAPK1 and MDR1). Moreover, *A. galangal* enhances p53 expression and apoptosis (Ahlina et al. 2020) and acts as an antiproliferative agent by triggering S phase arrest in the cell cycle (Raveesha et al. 2021). *A. galangal* boosted the lethal impacts of cytotoxic T-cells by reducing the abundance of human triple-negative cancerous cells (Alif et al. 2021). Further, *A. galangal* extract may also cause cell senescence, and its anti-proliferative effect against HER2-overexpressing breast cancer has been connected to internal ROS levels, delaying cell cycle progression (Jenie et al. 2021). In humans, the 1′-acetoxychavicol acetate constituent of AG suppressing the pERK1/2, pAKT, epidermal growth factor receptor 2, cyclin D1, estrogen receptor coactivator, and MYC proto-oncogene in a time and concentration-dependent manner (Jenie et al. 2021).

4.3 *Achillea wilhelmsii*

Plant *Achillea wilhelmsii* is a member of the Asteraceae family of the genus Compositaea. Leaf methanolic extract of this plant has cytotoxic effects on colon cancer cells line (HT-29). Various research has also demonstrated the benefits of plant leaf methanol extracts on colon, stomach, and breast cancer cell lineage. The methanolic extract of the plant has high concentrations of phenolic compounds mainly flavonoids inhibit cancer cell multiplication by triggering apoptosis. Kooti et al. (2017) reported that 1,8-cineole and a-piene isolated from the leaf essence of *A. wilhelmsii* are the two most significant monoterpene chemicals that trigger apoptosis in human melanoma cells.

4.4 *Camellia sinensis*

The buds and petals of this plant have been used for tea production. Tea leaves contain caffeine, thianin, and theophylline, like active ingredients, which are responsible for the antioxidant

properties of the tea leaves. Leaves of green tea also inhibited the production of 5-alfardoctase enzymes in mice. This enzyme transforms testosterone into dihydrotestosterone, a prostate cancer-causing substance. As a result, it has been found that green tea can help prevent prostate cancer (Wang et al. 2015). Green tea leaves are an essential source of epicatechin, epigallocatechin, and epigallocatechin-3 polyphenols which have anti-cancerous properties. Green tea's cytotoxic effect has also been reported against breast cancer cell lines. Drinking green tea regularly reduces the hazardous effect of stomach tumors (Srivastava et al. 2010).

4.5 *Ficus carica*

Ficus carica (FC) belongs to the family Moraceae, and this plant was initially endemic to West Asia & the Middle East. However, now it is prevalent in different parts of the word (Idrus et al. 2018). Numerous plant constituents are exploited for their medicinal properties in treating various ailments, including respiratory, inflammatory, cardiovascular, and gastrointestinal disorders (Bouyahya et al. 2016; Idrus et al. 2018). This plant also has antibacterial, antioxidant (Harzallah et al. 2016; Mahmoudi et al. 2016), anticancer (Hashemi and Abediankenari 2013; Tian et al. 2014), anti-acne (Vaghasiya et al. 2015), and antipyretic (Bouyahya et al., 2016) pharmacological properties. This plant species has several bioactive ingredients, like arabinose, amyrins, carotenes, glycosides, sitosterol, and xanthotoxol, which have various medicinal advantages (Figure 3). Zubair et al. (2015) reported significant cytotoxicity of ethyl acetate extract of *F. carica* against breast cancer (MCF-7) cell lines. By boosting the expression of proapoptotic (BAX) and tumor suppressor genes, the extract of FC leaves suppressed the growth of MDA-MB-231 cells (TP53 and TP21). In addition, Zhang et al. (2018) reported that FC extract administration decreased the breast cancer marker gene (GATA3) and also had an impact on the expression of exproto-oncogene (ELF5). Ghandehari and Fatemi (2018) reported that breast tumor volume and size decreased in rats treated with a latex extract of *F. carica*. Further, the histological study of fig latex-treated rat breast cells showed a reduction in angiogenesis, mitotic features, & necrosis. In another Lightbourn et al. (2008) study, *F. carica* leaves extract shortening the S and G2/M stages of the cell cycle and causing apoptosis by a p53-independent mechanism, also inhibited the spread of MDA-MB-231 mammary tumor cells (Sánchez-Valdeolívar et al. 2020). A combination of olive oil and fig extract demonstrated a cytotoxic effect against T-47D and MCF-7 cells (Widyaningrum et al. 2020; AlGhalban et al. 2021). The anticancer impact was detected in MDA-MB-231 cells, showing antiproliferative and antimetastatic activities of fig extract.

4.6 *Nigella sativa*

Nigella Sativa (NS) is a member of the family Ranunculaceae. It is considered a miraculous herb. Researchers have discovered many pharmacological characteristics, including anti-inflammatory (Ikhsan et al. 2018; Mokhtari-Zaer et al. 2020), antihypertensive (Lokeswara et al. 2019), antioxidant (Bordoni et al. 2019), antidiabetic (Bensiameur-Touati et al. 2017; El Rabey et al. 2017), antimicrobial (Bakal et al. 2017; Randhawa et al. 2017) and anti-cancerous properties (Czajkowska et al. 2017; Tabassum et al. 2018). Anti-cancerous action was demonstrated by the extra-expression of caspase-3, which is related to apoptosis in malignant tissue. The main active ingredients of this plant are monoterpenes, i.e., cumin aldehyde, 2-ethoxy-3-isopropylpyrazine, 3-sec-butylpyrazine, 2-methoxy-3-methylpyrazine, pinene, cuminic alcohol, pyrazines, 2-methoxy, terpinene, safranal, p-cymene, and thymoquinone, (Figure 3). The aqueous and crude extract of *N. Sativa* prevented the growth of MCF cell lines as efficiently as cisplatin (Elkady et al. 2015; Reddy et al. 2015). The histological examination of *N. Sativa* seed accompanied DMBA rats showed breast cell activation and inhibition of developing breast cancer cell proliferation. Thymoquinone was the main compound in *N. Sativa* seed oil, it decreased tumor volume, LDH, and MDA levels, and the activity of ALP and AST and this Thymoquinone (TQ) was found more effective than TT in suppressing the gene expression of Brca1 and Brca2 (Linjawi et al. 2015). Moreover, it significantly elevates the P53 gene expression (Dastjerdi et al. 2016). It has been established that the ultrasonic nanoemulsion formulation of *N. Sativa* essential oil induces apoptosis in MCF-7 cells and exhibits anticancer activity (Ma et al. 2008). According to Bumidin et al. (2018) *N. Sativa* extracts may decrease the integrity of MCF-7 cell membranes, inhibiting the development and viability of MCF-7 cells. Thymoquinone induces apoptosis via coordinating pro and anti-apoptotic gene expression. It suppresses metastatic development by activating JNK and p38 and lowering NF-kB and IKK/αβ phosphorylation (Imran et al. 2018). By regulating the development of Bax, Bcl-2, and COX-2, aqueous *N. Sativa* seed extract-derived silver nanoparticles (AgNPs) induce programmed cell death in MCF-7 cell lines (Rohini et al. 2019). Rafati et al. (2019) found that applying *N. sativa* gel, such as a prophylactic intervention, considerably prolonged and lowered the prevalence of ARD and moist desquamation in cancer tumor cases. Hydroalcoholic extract of *N. Sativa* suppressed breast cancer cell proliferation (MCF 7). A reduction in NF-kB and IKK mRNA expression levels demonstrated the anti-inflammatory effects of *N. Sativa* (Kordestani et al. 2020; Khurshid et al. 2020). *N. Sativa* extracted proteins have anti-proliferative and apoptotic activities on the human breast cancer cell line MCF-7. Further, H1047R and H1047L mutations can impair breast cancer's PIK3CA kinase domain regulation, resulting in increased PI3K/Akt1 pathway activation (Khurshid et al. 2020). Through suppressing autophagy, thymoquinone was found to limit the proliferation and metastasis of MDA-MB-231 cells (Zhou et al. 2022). The binding of *N. Sativa* isolated thymoquinone to the kinase domain of PI3CA mutants inhibits

TQ-mediated activation of the PI3K/Akt1 pathway. Further, *N. Sativa* seed oil drastically decreased cell proliferation and viability and worked as an anticancer and antiproliferative agent (Baig et al. 2022; Hussain et al. 2022).

4.7 Curcuma longa

Turmeric (*Curcuma longa*) is a plant of the Zingiberaceae family, and dried rhizomes of this plant are edible (Huseini et al. 2010). The cytotoxic activities of turmeric have been studied in liver cancer cells (Hep-2). It has been discovered that dose-dependent cytotoxicity of curcumin leads to cancer cell death via the mitochondrial route (Ayyadurai et al. 2013). In breast cancer, Ranjbari et al. (2014) research findings evaluated the impacts of turmeric extract on telomerase activity and found that telomerase has antiproliferative and inhibitory properties. Mohammad et al. (2010) have also discovered the cytotoxic impacts of turmeric on lung cancer cells by suppressing telomerase activity. Curcumin, a key component of turmeric, is vital in preventing and treating cervical cancer (Reda et al. 2020; Alagawany et al. 2021).

4.8 *Rosmarinus officinalis*

Rosmarinus officinalis, also known as rosemary, belongs to the family Lamiaceae. Hassani et al. (2016) reported that the seed oil of *R. officinalis* drastically decreases cell proliferation and viability so that it can act as an anticancer and antiproliferative agent. The pharmacological qualities of this plant included antioxidant and antibacterial (Takayama et al. 2016; Bajalan et al. 2017), anti-cancerous (Soundararajan et al. 2017), anti-inflammatory (Harris et al. 2019; Rocha et al. 2015) and antidiabetic properties (Ahamad et al. 2019; Belmouhoub et al. 2018). The anti-cancerous activity of this plant is associated with various phenolic acids such as quinic acid, caffeic acid, rosmarinic acid, and caffeoylquinic acids (Moore et al. 2016). *R. officinalis* essential oil reduced the viability of the MCF-7 cell line at a dose of 400 g/ml (IC50 = 48.01 0.94), as shown by the elevated concentrations of ADP-ribosyl polymerase (PARP) cleavage, a well-known marker for apoptosis (Tabatabaei et al. 2018). Farshchi et al. (2018) evaluated the cytotoxic impacts of *R. officinalis* aqueous extract green iron nanoparticles and reported an anti-proliferative effect with bleomycin medication (Mrdjanovic et al. 2019). Using 4T1 and MCF-7 cell lines, *R. officinalis* inhibited the growth and survival of MDA-MB-231 cells at low doses (0.5-20 µg/mL). It drastically decreased the protein kinase concentrations of Akt & mTOR, which are crucial growth and survival factors for cancer cells (Jaglanian 2019; Jaglanian and Tsiani 2020). RO ethanolic extract showed an antiproliferative impact against MCF-7 cancer cell lines (Shen et al. 2020). Mahmoud et al. (2021) also suggested that *R. officinalis* significantly reduced the phosphorylation/activation concentrations of Akt & mTOR at low levels (0.5-20 g/mL).

4.9 *Urtica dioica*

Urtica dioica (UD) is a widespread herb that belongs to the family Urticaceae and the genus Urtica (Badirzadeh et al. 2020). Various pharmacological activities such as anti-inflammatory (Liao et al. 2016), anticancer (Mohammadi et al. 2017), antirheumatic (Riehemann et al. 1999), cardiovascular (Saleem et al. 2002), antiaging, and antioxidant (Bourgeois et al. 2016) have been reported from this tree. The predominant flavonoids, including quercetin, 3-rutinosides, kaempferol, isoquercitrin, astragalin, rutin, isorhamnetin, and 3-glycosides were recorded from this plant (Figure 3) (Martínez-Aledo et al. 2020). DNA fragmentation and the TUNEL test revealed the harmful effect of *U. dioica* dichloromethane extract on the proliferation and spread of MDA-MB-468 cells. PCR found that apoptosis raised caspase-3 and caspase-9 mRNA expression levels while decreasing BCL-2. The research of Mansoori et al. (2017) lowered lipid peroxidation and increased the catalase enzyme activity in rat mammary carcinoma cells. Histological study showed that malignant animals treated with *U. dioica* had significant ductular proliferation and localized epithelial hyperplasia. Further, *U. dioica* extract can suppress the development and migration of mammary tumor cell lines in *in-vivo* models and regulate miR-21 gene expression of breast cancer (Telo et al. 2017). Real-Time PCR study demonstrated increased proapoptotic caspase three and caspase nine and a decrease in anti-apoptotic Bcl- 2. Akbarian et al. (2018) also reported cytotoxic impacts of *U. dioica* ZnO nanoparticles on MCF-7. Fattahi et al. (2018) analyzed ornithine decarboxylase (ODC1) and adenosine deaminase (ADA) gene expression to assess the anticancer impact of *U. dioica* aqueous extract on MCF-7 and MDA-MB-231 cell lines. They noticed that *U. dioica* stimulates apoptosis in mammary tumor cells by elevating the expression of ODC1 and ADA in MCF-7 cell lines. Further, 1200 g/ml of *U. dioica* hydroalcoholic extract reduces the number of MCF-7 cells (Soltani et al. 2021).

4.10 *Murraya koenigii*

Murraya koenigii (MK) is extensively distributed across Eastern Asia. This plant's diverse pharmacological effects are antifungal (Tripathi et al. 2018), antioxidant (Rehana et al. 2017; Tomar et al. 2017), antibacterial (Erkan et al. 2012), antidiabetic (Husna et al. 2018), anti-inflammatory (Iman et al. 2016; Mani et al. 2013) and anti-cancerous property (Yeap et al. 2015). This plant's active constituents include murrayanine, bi-koeniquinone-A, bismahanine, murrastifoline, murrayafoline-A, bismurrayaquinone, mukoenine-A,B,C, Murrayazolinol, murrayacine, and murrayazolidine (Figure 3) (Aniqa et al. 2022). *M. koenigii* aqueous extract dramatically lowered tumor size, and the histological qualities of *M. koenigii* leaf extract indicated its ability to control inflammation, reduce the number of tumor cells, and block tumor cell proliferation (Yeap et al. 2015). It also reduces

nitric oxide levels and inflammatory mediators cytokines and genes, enhancing T cell cytokine production, which aids in mitotic division reduction and delays breast cancer growth. Caspases-3 activity and TUNEL-positive cells enhanced after treatment with *M. koenigii* extract, indicating accelerated apoptosis (Noolu et al. 2016). Total alkaloid extract from *M. koenigii* reduced breast cancer cell viability (IC50 = 14.4 g/mL), altered development dynamics, arrested cells in the "S" stage, and induced cell death (MDA-MB-231) (Ismail et al. 2016). MTT assay showed the antitumor effectiveness of *M. koenigii* silver nanoparticles against breast cancer cell types (MDAMB-231). In rats with DMBA-generated breast cancers, the ethanolic extract of *M. koenigii* demonstrated anticancer activity (Vijapur et al. 2019). Significant reductions were seen in tumor volume, the number of polymorphonuclear leukocytes, multilayered cuboid epithelium, & the proliferation of solid collagen fibers following therapy with *M. koenigii* extracts (Aisyah et al. 2020). Additionally, Aisyah et al. (2021) discovered the elevation of caspase-3, which is related to apoptosis in malignant cells and has anticancer action. Mahanimbine, the active component of *M. koenigii*, has shown apoptotic and anti-angiogenic activity against breast cancer cells (Hobani 2022).

5 Plant Metabolites against cancer cell line

5.1 Colchicine

Colchicine is the secondary plant metabolite produced by *Gloriosa superba* and *Colchicum autumnale*. It induces mitotic binding during the cell cycle, making it a solid anti-mitotic medication in both *in-vitro* and *in-vivo* conditions. Colchicine extracts, such as 3-dimethyl colchicine, colchicoside, and thiocolchicocide, were created due to the severe toxic effects and demonstrated better effectiveness against some leukemic cells solid tumors (Sadooghi et al. 2013).

5.2 Podophyllotoxin

The roots of two *Podophyllum* species, *Podophyllum peltatum* L. and *Podophyllum emodi* Wallich contain podophyllotoxin. In the 1880s, it was dismantled, and its structure was explained in 1950. Epipodophyllotoxin is a podophyllotoxin isomer. Etoposide and Teniposide, two key therapeutic analogs derived from Epipodophyllotoxin, are highly successful in curing bronchial lymphomas, testicular cancer, leukemia, and ovarian cancer (Shoeb et al. 2006).

5.3 Taxanes

The Pacific Yew, *Taxus brevifolia* Nutt, contains paclitaxel (Taxol®) (Taxaceae). Their structure was initially discovered in 1971 and has been sold since the 1990s. *Taxus baccata*, an Ayurvedic medication from India, was also utilized to cure cancer (Kingston 2007). Because paclitaxel is insoluble in water and poisonous, another taxel, i.e., Docetaxel, a water-soluble molecule, was developed. Docetaxel (Taxotere®), a paclitaxel semi-synthetic product, is more effective. Docetaxel can be utilized for individuals resistant to paclitaxel (Kingston 2007). These medications are now accessible and can treat lung, prostate tumors, and lymphoid malignancies.

Conclusion and Further Perspectives

A rational and cost-effective solution for preventing a terrible illness like cancer exists. Daily use of herbs in infusions or meals may protect tissues from oxidative stress and prevent cancer development. Recent studies suggest that medicinal plants addressed in this study have anticancer properties. These plants can inhibit tumor volume and cell proliferation, enhance histoarchitecture, stimulate apoptosis, and interrupt cell-cycle in preclinical *in-vivo* and *in-vitro* models of breast cancer. To bring innovative commodities to market as either a chemopreventive drug or an anticancer treatment, however, clinical trials are essential to assess the impact of these herbs on humans.

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