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Some Medicinal Plants with Anti-breast Cancer Activity and the Input of Phytotherapy in the Treatment of Breast Cancer

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Abstract

Aim: Breast cancer is the most commonly diagnosed cancer leading to death among women worldwide. Despite the advances in the diagnosis skills and in the treatment of breast cancer, it has been observed that the recurrence rate experienced by breast cancer patients is quite high. Many plants have been reported to have anti-breast cancer properties. This paper focuses on determining the role of phytotherapy in the treatment of breast cancer.

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Methods: The following key search terms were used on Pubmed, Google scholar, and Researchgate: breast cancer, breast cancer cell lines, phytotherapy, medicinal plants in the treatment of breast cancer, treatment of breast cancer, cytotoxics effects of plant extracts on breast cancer *in vitro/ in vivo,* integrative oncology, and natural products as sources of drugs. Pertinent reviews in English language were examined.
Results: It has been observed that many studies were conducted *in vitro and in vivo* to demonstrate the anti-breast cancer activities of a myriad of plants. While investigations are being made to prove the anti-breast cancer effects of many plants, the use of phytomedicine is not generating enough attention by mainstream practitioners. Some significant results were observed by patients with breast cancer history through the combination of phytotherapy and conventional medicines.
Discussion: The conventional treatment of breast cancer is often accompanied with side effects. Many patients in low-income countries are faced off with the enormous cost of conventional treatment. Hence, there is a need to search for new bioactive substances in the treatments of breast cancer. Phytotherapy is a promising approach and herbal preparations are to be used in the same way as conventional medicine in the treatment of breast cancer.
Conclusion: Phytotherapeutics products are used more often in the treatment of breast cancer as adjuvant therapy. In Africa, the use of herbal products in the treatment of breast cancer still remains in the hands of traditional-practitioners, without any control of quality and efficacy. Standard methods for the preparation of herbal products are to be determined in order to adopt phytotherapy in the treatment of breast cancer as much as conventional treatment.

Keywords: Breast cancer, phytotherapy, anti-breast cancer properties, plant extracts

Introduction

Breast cancer is the most common cancer in women worldwide (Ferlay et al., 2019). Over 2.3 million new cases and 685,000 deaths from breast cancer occurred in 2020 (Arnold et al., 2022). The management of breast cancer has seen significant advancements in recent decades, with various approaches such as surgery, hormone therapy, chemotherapy, radiation therapy, and immunotherapy being employed to combat this condition. Nonetheless, the treatment faces substantial challenges in terms of its expense, adverse effects, and the systemic toxicity associated with existing chemotherapeutic agents, along with the development of drug resistance (Kingham et al., 2013). Natural products and their structural analogues have historically made a major contribution to pharmacotherapy, especially for

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cancer and infectious diseases (Atanasov et al., 2021). The recognition of medicinal plants as effective and inexpensive sources of synthetic novel chemotherapeutic compounds is increasing in the last decades and many researchers focus their research on this promising area (Omogbadegun, 2013). For example, in the area of cancer, over the time frame from 1981 to 2019, out of the 185 small molecules used for the treatments of cancer, 62 or 33.5% are natural compounds. However, adding 58 natural products such as pharmacophore and pharmacophore/mimic brings the figure to 64.9% (Newman et al., 2020). It has been noticed that most of time, patients use plant products for self-medication (Rossi et al., 2015). They use products derived from all or parts of plants and this is a common practice in all civilizations around the world including Asia, Africa, Europe, and America (Rossi et al., 2015). Herbal-based and plant-derived products can be thus exploited with sustainable comparative and competitive advantages, especially in developing countries to reduce the exorbitant cost of breast cancer treatment. This study presents an overview of the input of phytotherapy in the treatment of breast cancer.

1. Methods

For the elaboration of this study, the under listed key words were searched on Pubmed, Google scholar, and Researchgate: breast cancer, breast cancer cell lines, phytotherapy, medicinal plants in the treatment of breast cancer, treatment of breast cancer, cytotoxics effects of plant extracts on breast cancer *in vitro/ in vivo*, integrative oncology, and natural products as sources of drugs. Searches were limited to articles in English language. 369 articles that were published from 1993 to 2023 were identified. After extracting 150 articles, the remaining 219 pertinent articles were scrutinized.

2. Results

2.1 Plants Products as Adjuvant Therapy in the Treatment of Breast Cancer

Conventional treatment of breast cancer may include surgery, radiation, chemotherapy, and hormone therapy. The stage of diagnosis influences both the prognosis and the treatment strategies for breast cancer. Breast cancer is usually treated by combining surgery with radiation, chemotherapy, and hormone therapy, whereby surgery is usually the first step in cancer treatment (Ma et al., 2011). However, the conventional treatment is often coupled with severe side effects such as nausea, fatigue, vomiting, and hair loss. Furthermore, with patient survival rates increasing, oncologists and other therapists have to become more sensitive to the needs of breast cancer survivors, which goes beyond the mere alleviation of symptoms (Ma et al., 2011).

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A new trend in the breast cancer therapy is the combination of the conventional and complementary alternative medicine (CAM). Breast cancer survivors who combine the standard medicine, namely, chemotherapy and radiotherapy with the complementary are increasing (Ma et al., 2011). "Complementary" or "alternative" medicine refers to the methods advocated by other medical approaches, which include a multitude of diverse medical and health care systems, practices and products, not generally considered as part of conventional medicine (Ma et al., 2011). Among CAM treatments, herbal preparations or phytotherapy are commonly used to treat cancer patients (Ma et al., 2011). Generally, phytotherapeutic products were used as a combination therapy with the conventional chemotherapy to hopefully increase the therapeutic benefit and quality of life (QoL), as well as to decrease the side effects or complications of the conventional medicine (Nagykalnai et al., 2014). In the breast cancer domain, the biological effects of herbal medicinal products could be diverse (Nagykalnai et al., 2014). It can be used as defence against malignancy by increasing detoxification or cleaning and modification of the action of some hormones and enzymes (Rossi et al., 2015). Phytotherapeutic products are also used to reduce the side effects and complications of chemotherapy and radiotherapy (Rossi et al., 2015). Herbal preparations help improve the function of the body's immune cells (i.e., stimulation of the production of cytokines including interleukin, interferon, tumour necrosis factor, and colony stimulating factor) (Rossi et al., 2015). It has been identified by the National Cancer Institute that several commonly used herbs possess cancer-preventive properties. These include members of the Allium sp. [garlic, onions and chives], members of the Labiatae family [basil, mints, oregano, rosemary, sage, and thyme], members of the Zingiberaceae family [turmeric and ginger], and members of the Umbelliferae family (anise, caraway, celery, chervil, cilantro, coriander, cumin, dill, fennel, and parsley) (Chan et al., 1993). Curcumin, a polyphenolic compound, is a secondary metabolite isolated from the rhizomes of turmeric. It exhibits a number of therapeutic effects, including anti-cancer properties, via modulating different molecular regulators (Shanmugam et al., 2015; Devassy et al., 2015). Several clinical studies researched the effects of curcumin in breast cancer. In a randomized, double-blind, placebo-controlled clinical trial, oral curcumin (6.0 g/day) during radiotherapy was found to reduce the severity of radiation dermatitis in breast cancer patients (Ryan et al., 2013). Another study showed that curcumin could be used as an in *vivo* inhibitor of breast cancer resistance protein (Kusuhara et al., 2012). Bayet-Robert et al. (2010) recommended a daily dose of 6000 mg of curcumin for seven consecutive days every 3 weeks in combination with a standard dose of docetaxel for the combination therapy in advanced and metastatic breast cancer patients. Garlic has been indicated to mitigate the adverse effects of several anticancer therapies (Raisuddin et al.,

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2018). Allicin, a bioactive compound of garlic has been found to enhance the anticancer effect of tamoxifen in mice and reduce the liver injury caused by tamoxifen treatment. Allicin also improved the tamoxifen-induced changes in the levels of superoxide dismutase, glutathione, aspartate aminotransferase, alkaline phosphatase, and alanine aminotransferase (Nasr et al., 2014). Onion *(Allium cepa)* and scallion *(Allium fistulosum)* were also included in *Allium* genus, which showed cancer-preventive effects, attributed to sulfur-containing compounds (Nicastro et al., 2015). In addition, there are also other constituents in onion, such as quercetin and fisetin which possess anticancer effects. Fisetin showed cancer-preventive effects via modulating the PI3K/Akt/mTOR pathway in cancer cell models (Syed et al., 2013) and in animal models (Khan et al., 2013). Ginger (*Zingiber officinale*) is rich in several bioactive phenolics, including non-volatile pungent compounds such as gingerols, paradols, and shogaols (Karna et al., 2012) which possess anticarcinogenic proprieties (Prasad et al., 2015; Haniadka et al., 2012; Pereira et al., 2011). Cancer development and progression could be decreased by 6-shogaol via inhibiting the production of inflammatory mediator chemokine (C-C motif) ligand 2 (CCL2), derived from breast tumor-associated dendritic cells (TADCs) (Hsu et al., 2015). A clinical trial showed that inhaled ginger aromatherapy might be a complementary therapy for chemotherapy-induced nausea and vomiting in women with breast cancer (Lua et al., 2015).

Many herbs contain a variety of phytosterols, triterpenes, flavonoids, saponins, and carotenoids, which have been shown from studies of legumes, fruit, and vegetables to be cancer chemoprotective (Nishimura et al., 1993). Vegetable and fruits have a high content of healthy components such as vitamins, minerals, and fibers. Subsequently, phytoconstituents resulting from herbs such as *Vinca rosea, Taxus species, Allium sativum, Aloe vera, Angelica sinensis, Astragals membranaceus, Glycine max, Glycyrrhiza glabra, Hordeum vulgare, Hydrocotyle asiatica, Medicago sativa, Morinda citrifolia, Panax pseudoginseng, Saussurea lappa, Taxus wallichiana, Tinospora cordifolia, Viscum album, Withania somnifera, Zingiber officinale* etc. have been used in numerous preparations to improve function of the body's immune cells that stimulates production of cytokines including interleukin, interferon, tumor necrosis factor, and colony stimulating factor. These preparations assist the body to battle cancer more efficiently and also decrease the harmful side effects of chemotherapy and radiotherapy (Sabarkar & Deshmukh, 2011). According to a meta-analysis, the combined prevalence for "current use" of complementary and alternative medicine (CAM) by patients with cancer is 40% (Horneber et al., 2012). In the past few years, this rate seems to have increased, with more than 90% of patients with breast cancer using some type of CAM. Nonetheless, a high heterogeneity exists between Western countries with respect to CAM usage. Thus, the United States are regarded as the highest

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while Italy and the Netherlands are identified as the lowest (Horneber et al., 2012). Dobos et al. (2012) reported the practice of the concept of integrative oncology for breast cancer patients by German cancer centres such as the Department of Internal and Integrative Medicine, Kliniken Essen-Mitte, academic teaching hospital of the University of Duisburg-Essen, and the Breast Centre at Kliniken Essen-Mitte (Dobos et al., 2012). In Africa, despite the heterogeneous nature of the continent and a deluge of information on the composition and biological activity of many plant substances, few efforts have been devoted to the development of chemotherapeutic and prophylactic agents from plants. Therefore, many breast cancer patients in Africa use plant products for self-medication. However, many studies on the anti-breast cancer properties of plants used in traditional medicine have been carried out on the African continent. Zengue et al. (2018) demonstrated that the ethanolic extract of *Acacia Seyal* stem bark has cytotoxic effects against a variety of tumor cells. Furthermore, it protected rats against DMBA-induced breast hyperplasia as well as breast tumor incidence, with an optimal effect at the dose of 300 mg/kg (Zengue et al., 2018). Bassong et al. (2022) examined the effects of *Hibiscus Sabdariffa* Calyxes Aqueous Extract on Antioxidant Status and Histopathology in Mammary Tumor induced rats. They found out that *Hibiscus sabdariffa* calyxes aqueous extract reduced animal death, tumor incidence, tumor burden and volume, as well as the level of breast cancer biomarker CA 15-3. This implies that rats were protected against diffuse breast neoplasia induced by DMBA.

In addition, this extract showed antioxidant effects characterized by a decrease in the Malondialdehyde level and a significant increase in the activity of superoxide dismutate (Bassong et al., 2022). Kuete et al. (2011) tested the cytotoxity effect of two compounds, xanthone V_1 and 2-acetylfuro-1,4-naphthoquinone, isolated from cameroonian medicinal plants, *Visma laurentii* and *Newbouldia leavis*. The study provided evidence for the cytotoxicity of compounds xanthone V_1 and 2-acetylfuro-1,4-naphthoquinone (Kuete et al., 2011).

2.2 Overview of Some Selected Plants With Anti-breast Cancer Activities

Natural compounds with potent anti-cancer activities are widely available from different plant tissues. Eighty percent (80%) of the population worldwide traditionally use natural compounds contained in medicinal plants (Fulda, 2010). Therefore, investigations are being made to determine the anti-proliferative activity of many plant extracts. It has been found that multiple plant products exist that have shown very promising anti-breast cancer properties *in vitro* and *in vivo*. This is an overview of some selected plants with anti-breast cancer activities.

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a. Vernonia amygdalina

Vernonia amygdalina (*compositae*) is a small shrub that grows predominantly in tropical Africa. The macerated leaves of the plant are used in making soup while the water extract serves as a tonic drink for the prevention of certain illnesses (Thirumal et al., 2012). *V. amygdalina* had been reported to possess several pharmacological effects such as antimicrobial, antimalarial, antithrombotic, antioxidant, anti-diabetic, laxative, *hypoglycemic*, antihelmintic, anti-inflammatory, cathartic, anticancer, antifertility, antifungi, and antibacterial, among others (Alara et al., 2017). *Vernonia amygdalina* ethanol leaves extracts were found to inhibit the proliferation of MCF-7 and MDA-MB-231, which involved the stimulation of cell-type specific G1/S phase cell cycle arrest in only MCF-7 cells but not in MDA MB-231 cells. This is because an approximate of 70% of diagnosed breast cancer express ER-α (Wong et al., 2013). Joseph et al. (2021) demonstrated that the ethanol leaves extract and *V. Amydalina* silver nanoparticles inhibit MCF-7 cell proliferation with an average half-maximal inhibitory concentration (IC50) value of 67µg/ml and 6.11µg/ ml after 72 hours of treatment respectively. The ethanol leaves extract and *Vernonia Amygdalina* silver nanoparticles also caused G1 phase cell cycle arrest, induced apoptosis, and nuclear fragmentation in MCF7 cells (Joseph et al., 2021). Further research is needed to highlight the difference in mechanisms of action for both treatments. There is also a need to investigate the mechanism of action of the *Vernonia Amigdalina* silver nanoparticles in drug delivery due to its enhanced potency when compared to *Vernonia Amygdalina* ethanol extract (Joseph et al., 2021).

b. Solanum torvum

Solanum torvum (*S. Torvum*) belongs to *Solanaceae* (nightshade family) and is a spiny herb or shrub 3-4 meters tall. It is found throughout the tropical parts of India and in Andaman. The leaves are ovate, sinate or bilobed, lobes are shallow, rarely deep, and flowers are white, in dense lateral racemes. Its berries are smooth, yellow or orange and the seeds are smooth as well (Nawal & Atta, 2013). Various preparations based on *S. Torvum* fruits, seeds or vegetative parts are indeed reported to be effective medicines against fever, cough, wounds, pain, liver troubles, tooth decay, reproductive problems, arterial hypertension, and poisoning (used as antidote) (Ndebia et al., 2007; Mohan et al., 2010). The fruits and root extracts of *S. torvum* was found to be extremely effective in the prevention of cell proliferation of the mammary gland breast adenocarcinoma cell lines (Nawal & Atta, 2013).

Furthermore, Nunuk et al. (2020) demonstrated that the ethyl acetat fraction of *solanum torvum* fruit has the best cytotoxic activity on T47D breast cancer cells. Among the ten best compounds identified from GC–MS analysis of

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aqueous extract of unripe fruits of *solanum torvum* against breast cancer target protein BRCA1, three compounds showed very good binding affinity with breast cancer target protein. These include ergost-25-ene-3,6-dione,5,12-dihydroxy-,(5.alpha.,12.beta.) (−7.3 kcal/mol), aspidospermidin-17-ol,1-acetyl-16-methoxy (−6.7 kcal/mol), and 2-(3,4-dichlorophenyl)-4-[[2-[1-methyl-2-pyrrolidinyl] ethyl amino]-6-[trichloromethyl]-s-triazine (−6.7 kcal/mol) (Saravanan et al., 2022). Also, docking study was performed for the synthetic drug doxorubicin to compare the efficiency of phytocompounds. The binding affinity of ergost-25-ene-3,6-dione,5,12-dihydroxy-,(5. alpha.,12.beta.) is higher than the synthetic drug doxorubicin (−7.2 kcal/mol), and the binding affinity of other compounds is also very near to the drug. Hence, the phytocompounds from the aqueous extract of *Solanum torvum* unripe fruits have the potential ability to treat breast cancer (Saravanan et al., 2022). Notwithstanding, further studies are needed to develop standard trial mechanism for the use of the isolated compounds/herbal preparations of unripe fruits of *solanum Torvum* as drug in the treatment of breast cancer.

c. Avicennia marina

Avicennia marina is a mangrove species of the Acanthaceae family, and discoveries of its chemical compounds have received much attention (Fardin et al., 2015). *A. marina* has been used as a traditional medicine for the treatment of skin diseases, rheumatism, ulcers, and smallpox. *In vitro* antimalarial, antibacterial, analgesic, and cytotoxic activities of *A. marina* have been reported (Bhimba et al., 2012). The ethyl acetate extracts of *A. marina* leaves have the highest phenolic and flavonoid contents and anticancer activities. It also showed higher cytotoxic effects. Hence, its leaves extracts suppressed xenograft MDA-MB-231 tumor growth in nude mice, thus suggesting that ethyl acetate extracts of *A. marina leaves* may provide a useful treatment for breast cancer (Huang et al., 2016*).* Ethyl acetate extract of *A. marina leaves* and stems displayed, after 48 h, 65% and 75% growth inhibition of the breast adenocarcinoma cell line MCF-7, at 100 µg/ml and 200 µg/ml, respectively. Furthermore, 100 µg/ml of the extract showed 10% apoptosis at 24 h, while no increasing value in apoptosis was found at 48 h or at 72 h. Nevertheless, increasing the extract concentration to 200 µg/ml displayed 25% apoptosis at 24 h, with an increase of 55% and 75% at 48 h and 72 h, respectively (Esau et al., 2015). Eldohaji et al. (2021) isolated lupeol, a pentacyclic triterpenoid, from hexane extract of *A. marina* stems, which caused considerable ($p < 0.001$) growth inhibitory activity on breast MCF-7 (45%) cell lines, with slight toxic effects on normal fibroblast cells (F180). The number of compounds isolated from *A. marina* extracts and tested against cancer cell lines is still limited. This encourages further investigation in this

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context to find new, natural, active molecules extracted from *A. marina* that can be employed as new drugs in cancer treatments (Cerri et al., 2022).

d. Annona muricata

Annona muricata is a lowland tropical, fruit-bearing tree of the Annonaceae family. It is found in the rainforests of Africa, South America, and Southeast Asia. *A. muricata*, commonly known as soursop, graviola, guanabana, or Brazilian paw-paw, has large, glossy, dark green leaves with edible, green heart-shaped fruits (Moghadamtousi et al., 2015). *A. muricata* preparations have been utilized to treat numerous ailments, making this plant an ethnomedically important species.

In developing tropical countries, including Africa, different parts of *A. muricata* are being used to treat conditions such as diabetes, coughs, skin diseases, and cancers (Liu et al., 2016; Yang et al., 2015; Syed et al., 2016). Endrini et al. (2014) showed that the ethanolic extract of soursop leaves displayed cytotoxic effects against MCF-7 within 24 and 48 hours incubation time, with IC50 values of 88.788 μg/ml and 14.678 μg/ml, respectively. Alshaeri et al. (2020) demonstrated that *Annona muricata* ethyl acetate leaves extract decreased the cell viability of BT-20 triple negative breast cancer in a concentration and time-dependent manner. The concentration of 10 μg/ ml had the greatest inhibition on cellular viability (23.7%, 10.9%, and 11.2% for 24, 48, and 72 h, respectively). The antiproliferative influence of *Annona muricata* ethyl acetate leaves extract is produced through EGFR-mediated signaling pathways, which include AKT, MAPK, NF-κB, and cyclin D1 inhibition. Further studies will be required to demonstrate the possible applications of this natural product in breast cancer therapy (Alshaeri et al., 2020).

e. Moringa Oleifera

Moringa oleifera L(MO) (Family: Moringaceae) is a perennial angiosperm plant, which includes several other species (Olson, 2002). It is a native of the Himalayan region that is widely cultivated throughout tropical and sub-tropical countries of the world, including Saudi Arabia (Alaklabi, 2015; Mbikay, 2012). Study showed the remarkable effects of Moringa leaves and bark on MDA-MB-231, ER-, and PgR+ breast cancer cell line. The extracts of leaves and bark tested in a study induced a significant level of apoptosis (Al-Asmari et al., 2015). Adebayo et al. (2017) found that the ethanolic extract of *Moringa Oleifera* seed significantly inhibited the proliferation of the MCF7 cell line. Elsayed et al. (2015) also found that seed essential oil from M. oleifera has potent cytotoxic activities against MCF-7 cell lines. However, its specific mechanism needs further research and determination (Wu et al., 2021).

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f. Glycyrrhiza glabra

Glycyrrhiza glabra is one of the most popular medicinal plants belonging to the Fabaceae family (also known as Leguminosae), and its members are now commonly used as feed and food. The genus *Glycyrrhiza* is derived from the Greek words *glykos* (sweet) and *rhiza* (root). This species is a native of Mediterranean areas, but it is now also present in India, Russia, and China. The extracts are currently used in pharmaceutical and food industries, as well as in the manufacture of functional foods and food supplements (Hayashi et al., 2009; Herrera et al., 2009). Different studies suggest that the extract of *G. glabra* may be a potential supplemental source for different cancer treatments (Lee et al., 2008). The bioactive components of the root extracts of *Glycyrrhiza glabra* have shown anti-cancer properties in both in *vivo* and in *vitro* studies (Sharma et al., 2018). 18-β-glycyrrhetinic acid and glycyrrhizic acids present in Glycyrrhiza are responsible for this property, which generally induces mitochondrial permeability transition and results to tumor cell apoptosis (Lee et al., 2008). Futhermore, Wang et al. (2015) demonstrated that glycyrrhizic acid effectively inhibits breast cancer cell MMP-2/MMP-9 expression and regulates the levels of Fra-1 and c-Jun, which are two main components of AP1 transcription complex in invasive breast cancer cells. This, in turn, suppresses breast tumor outgrowth (Wang et al., 2015). Nonetheless, further studies are needed to determine the use of the isolated compounds in the breast cancer therapy.

g. Curcuma Longa

Curcuma longa is a plant from the Zingiberaceae family. This perennial plant usually requires humid and rainy environment. The main habitat of Curcuma longa is hot areas of Asia such as India, Pakistan, Indonesia, and southern China, and it is a native of Africa and South America. Curcuma longa has underground stems called rhizome. Several aerial shoots as high as 1 to 1.5 m exit from these rhizomes (Fallah et al., 2010). Edible part of turmeric is dried rhizomes. The rhizome extract showed anti-proliferative and inhibitory effects of telomerase activity in breast cancer cells (Ranjbari et al., 2014). Curcumin, a chemical compound isolated from the rhizomes of *Curcuma Longa* has been reported to possess anticarcinogenic and antiproliferative activities in a broad spectrum of tumor tissues and animals. Additionally, current studies reveal that curcumin when used in combination with other anticancer drugs can efficiently induce apoptosis (Pröhl et al., 2016; Ananthakrishnan et al., 2012; Koohpar et al., 2015). However, its poor bioavailability and poor pharmacokinetic profile in a clinical application result shows its low anticancer potency. In this context, curcumin-related derivatives pose a new-platform for chemotherapy, and it is evident that curcumin derivatives overcome the aforementioned limitations and improve therapeutic

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efficacy. It has been demonstrated that the heterocyclic curcumin-based derivative exhibited remarkable anticancer activity against MCF-7 cell line, which displayed *in vitro* cytotoxic activity with an IC50 value of 20 µg/mL for the MCF-7 cell line (Mbeze et al., 2019). More studies are required to evaluate the mechanism of action of heterocyclic curcumin-based derivative.

h. Morinda Citrofolia L.

Morinda citrifolia L. commonly known as Noni is one of the species in the Rubiaceae family and is the only widely distributed member of the pantropical genus Morinda sensu stricto (Rubiaceae) (Razafimandimbison et al., 2010). It is widely distributed in the tropics including Indonesia, the United States, Brazil, Tahiti, Malaysia, and Australia. Seeds, bark, leaves, roots, and flowers are used in the treatment, but the fruits are considered to contain the most valuable chemical compounds (Assi et al., 2017). *Morinda citrifolia L*. has long been used by various ethnic groups in Indonesia and other countries as food or as a medicinal ingredient. MC can be used as a food supplement, functional food ingredient, or as a natural health enhancer all over the world (Assi et al., 2017). Noni has activity as an antibacterial, antiviral, antifungal, antitumor, anthelmintic, analgesic, hypotensive, anti-inflammatory, and immune enhancing effect (Singh, 2012; Assi et al., 2017). The ethyl acetate extract of the fruit of *Morinda Citrofolia L.* showed a higher order of *in vitro* anticancer activity profile. It strongly inhibited the proliferation of MCF-7 and MDA-MB-231 cell lines with IC50 values of 25 and 35 µg/ml, respectively. Although there was increase in apoptotic cells in MCF-7 and MDA-MB-231 cells, the cell cycle was arrested in the G1/S phase in MCF-7 and G0/G1 phase in MDA-MB-231 cells. The ethyl acetate extract of the fruit also decreases the intracellular ROS generation and mitochondrial membrane potential (Sharma et al., 2016). An anthraquinone isolated from the roots of *Morinda citrifolia L*., nordamnacanthal, was found to possess cytotoxic effects on MDA-MB231, MCF-7 and 4T1 cells *in vitro*. In addition, based on the cell cycle and Annexin V results, nordamnacanthal managed to induce cell death in both MDA-MB231 and MCF-7 cells (Abu et al., 2018). However, no mortality, signs of toxicity, and changes of serum liver profile were observed in nordamnacanthal treated mice in the subchronic toxicity study. Furthermore, different models of antitumor studies can support the potential of nordamnacanthal for treatment of breast cancer (Abu et al., 2018).

i. Melissa Officinalis L.

Melissa officinalis L. (MO), a perennial aromatic plant belonging to the Lamiaceae family, also called lemon balm due to its lemon scent, commonly grows in the Mediterranean region and Western Asia. It is intensively cultivated in Europe (Shakeri et al., 2016; Perez-Sanchez et al.,

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2016). For more than 2000 years, MO has been used as culinary herb and traditionally recommended as sedative, anxiolytic, antistress, antispasmodic, digestive, antimicrobial, and antiviral remedy (Caleja et al., 2017). Traditional uses from Europe are mainly linked to treating nervous ailments, insomnia, melancholia, and digestive and cardiac symptoms (Shakeri et al., 2016). The potential anticancer effects of lemon balm were previously studied using several types of extracts on various tumor cells. Breast cancer, next to lungs, prostate, or colon cancer, is among the most investigated types of cancer, particularly *in vitro* (Magalhaes et al., 2018; Encalada et al., 2011), but also *in vivo* (Saraydin et al., 2012). Some studies reported that alcoholic extracts were more effective than hydroalcoholic extracts against certain types of tumor cells, such as the hormone dependent MCF7 breast cancer cells (Magalhaes et al., 2018). On the other hand, others highlighted the sensitivity of MCF7 cell line to MO hydroalcoholic extracts (Jahanban-Esfahlan et al., 2015). In addition, MO aqueous extracts were proven to be effective against hormone-dependent (MCF7 cell line) and non-dependent (MDA-MB-468 and MDA-MB-231 cell lines) breast cancers (Saraydin et al., 2012). Ghiulai et al. (2020) showed that 96% ethanolic leaves extract of *Melissa Officinalis L.*, with a higher concentration of Ursolic Acid, has the highest cell inhibitory activity in particular against the estrogen receptor positive MCF7 breast cancer cell line, with no cytotoxic effect on healthy cells comparing with the methanolic extract. The estrogen receptor positive MCF7 cell line proved to be more sensitive to the extract antiproliferative activity than the triple negative MDA-MB-231 breast cancer cell line (Ghiulai et al., 2020). Further studies are to be conducted to determine the way to integrate *Melissa Officinalis L.* in the treatment of breast cancer.

j. Newbouldia Laevis

Newbouldia laevis (Seem. or Boundary Tree) is a medium sized angiosperm and tropical plant belonging to the family of Bignoniaceae. It often grows to a height of about 7-20 m, depending on the region where it was found. The stem also grows vertically with few branches. It is widely used traditionally for the treatment of malaria, prostate cancer, wounds, and eye problems (Nwauzoma & Dappa, 2013). Okeke et al. (2023) evaluated the chemo-preventive activity of ethanolic extracts of *Newbouldia laevis* leaaves on methylnitrosourea (MNU)–induced stroma fibrosis in female albino rats. It has been found that the ethanolic extract of *Newbouldia laevis* leaves have chemo-preventive activity in NMU-induced stroma fibrosis in the breast tissue of female albino rats. However, more studies on the discovery and validation of bioactive components of the plants are needed (Okeke et al., 2023).

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k. Olax subscorpioidea

Olax subscorpioidea is a shrub belonging to the family of Olacaceae, usually up to 10m high bole and 60 cm girth with long thin, drooping branches, of deciduous forest (Ahmad et al., 2021). It has been documented as part of traditional recipe for the treatment of various diseases in Africa. It possesses anti-oxidant, anti-inflammatory and anti-proliferative, anti-asthma, anti-diabetes, anti-cancer, antirheumatism, and anti-typhoid property (Kazeem et al., 2015; Poopla et al., 2021). It has been showed that the ethanolic leaves extract of *Olax subscorpioidea* significantly ($p < 0.05$) ameliorated CA 15-3, CA 27-29, and CEA levels in methylnitrosourea (MNU)–induced stroma fibrosis of female albino rats. Supplementary researches are needed for the validation and discovery of the bioactive molecules (Okeke et al., 2023).

l. Hibiscus Sabdariffa

Hibiscus sabdariffa (Malvaceae) also known as Roselle, sour tea, or karkade is a tropical wild plant (Sindi et al., 2014). It is native to West and Central Africa, growing in many tropics and subtropics. It is an annual, bushy, herbaceous plant characterized by red flowers and cylindrical stems (Da Costa-Rocha et al., 2014). The calyces of *H. sabdariffa* (HS) are used to give color and flavour to beverages, jam, flavouring agents, and jellies and are popular for making herbal tea mixtures (Nguyen et al., 2020). The HS is used traditionally for a variety of ailments including hypertension, liver disease, nerve disorders, alleviating constipation, and for the promotion of blood circulation. It is a medicinal plant known for its high content of bioactive compounds, such as polyphenolic acids, anthocyanins, flavonoids, amino acids, and minerals (Patel et al., 2014). Studies have shown that HS exhibits antioxidant activities and could be a potential medicinal plant for the development of novel therapies against cancer (Nguyen et al., 2020; Patel et al., 2014). It was demonstrated that the decoction of *H. Sabdariffa* (125 and 250 mg/kg BW) reduced tumor incidence *in vitro* by 63% and 75%, respectively. It further inhibited tumor burden by 84.86% and 38.78%, respectively (Bassong et al., 2022). Malacrida et al. (2022) evaluated the antitumoral effects of *Hibiscus sabdariffa* ethyl acetate calyces extract in human breast cancer cell lines, MCF-7(ERα +), and MDA-MB-231 (triple negative). They concluded that the *Hibiscus sabdariffa* ethyl acetate calyces extract is more effective on MCF-7 cells than MDA-MB-231 cells. Finding of the studies showed that the *Hibiscus sabdariffa* ethyl acetate calyces extract induced ERα trans-location from nucleus to perinuclear area and in cytoplasmic compartment. However, qRT-PCR and western blotting highlighted that the *Hibiscus sabdariffa* ethyl acetate calyces extract reduced ERα, BRCA1, and caveolin1 gene and protein expression in MCF-7 cells, but

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not in MDA-MB-231 cells. Further studies are necessary to deepen its mechanism of action (Malacrida et al., 2022).

m. Artemisia absinthium L.

Artemisia absinthium L. (wormwood) is a perennial herb found all over the world. In ethnic medicine, it is used as a vermifuge, insecticide and also has antiparasitic, antispasmodic, and antiseptic effects (Mughees et al., 2018). It is also used in the treatment of chronic fevers, inflammation of the liver, anorexia, and indigestion. The aerial part crude extract of the *A. absinthium* has shown inhibition of cell proliferation and induction of apoptosis in the breast cancer cell lines MCF-7 and MDA-MB-231. Hence, Treatment with 25 μg/ml crude extract of the *A. absinthium* resulted in activation of caspase-7 and upregulation of Bad in MCF-7 cells, while exposure to 20 μg/ml crude extract of the *A. absinthium* induced upregulation of Bcl-2 protein in a time-dependent response in MDA-MB-231 cells (Shafi et al., 2012). The active compounds viz. artemisinic acid and alpha thujone are present in different parts of this plant (Mughees et al., 2018). Subsequently, the hot methanolic leaves extract of *Artemisia absinthium L.* was actively inhibiting the proliferation of breast cancer cells MCF-7 at the concentration of 80.96 ± 3.94 μg/ml as IC50 value (Sultan et al., 2020). *Artemisia absinthium L.* proved to have anti-breast cancer properties that can be exploited in further studies.

n. Piper Nigrum

Piper nigrum is a perennial climbing herb native to the Malabar Coast of India. The herb grows up to a height of 10 m by means of its aerial roots (Meghwal et al., 2013). *Piper nigrum* (Piperaceae family) is a valuable medicinal plant. It is one of the most commonly used spices considered as "The King of spices'' among various spices. Black pepper is grown in many tropical regions (Ahmad et al., 2012).

The black pepper fruits, which are obtained from dried green unripe drupe and seeds have been extensively used in folk medicine to treat conditions ranging from gastrointestinal diseases to epilepsy (Meghwal et al., 2013). Sriwiriyajan et al. (2014) showed that alkaloid fraction without piperine of the dichloromethane crude extract had a significant pro-apoptotic activity (Sriwiriyajan et al., 2014). The crude extract of piperine free P. nigrum (PFPE) was found to up-regulate p53 and down-regulate estrogen receptor (ER), E-cadherin (E-cad), matrix metalloproteinase 9 (MMP-9), matrix metalloproteinase 2 (MMP-2), c-Myc, and vascular endothelial growth factor (VEGF) levels in breast cancer rats. Furthermore, PFPE decreased protein levels of E-cad, c-Myc, and VEGF in MCF-7 cells. These results suggest that PFPE can enhance breast cancer cell response to phytochemical, induce cell

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cycle arrest, and inhibit cancer cell proliferation (Deng et al., 2016). In addition, PFPE possessed cancer prevention effects through generation of reactive oxygen species (ROS) to higher cancer cell cellular stress (Deng et al., 2016). PFPE attenuated the side effects of doxorubicin (Saetang et al., 2022). Hence, further studies are necessary to determine the use of PFPE in the treatment of breast cancer.

o. Terminalia Chebula

Terminalia Chebula is a prime medicinal plant known as "Harard" in Indian sub-continent (Batt et al., 2017). It is a native tree of India, Bangladesh, Myanmar, Nepal, Pakistan, Vietnam, and South Western China (Akbar et al., 2020). *Terminalia chebula* was known as the king of medicinal plants in Ayurveda due to its utilization in herbal decoctions to treat various health disparities (Cock et al., 2015). The unripe fruit is most valued for its astringent and aperient properties, which is useful in handling dysentery and diarrhea. The ripened fruit is also used to improve the health of the gastrointestinal tract due to its purgative nature and adsorption ability. The Unani physicians consider it as tonic for the brain, memory, and vision. Furthermore, it was utilized in the treatment of diarrhea, piles, headache, epilepsy, and to purge yellow bile (Akbar et al., 2020). Ethanol fruit extract of *Terminalia chebula* exhibited prominent anticancer activity against breast cancer (MCF-7), with significant IC50 value of 228.82 µg (Sanakoussar et al., 2022). Furthermore, the homeopathic preparations of *Terminalia chebula* decreased the viability of breast cancer (MDA-MB-231 and MCF-7) (Wani et al., 2016). The MnO_2 NPs derived from *Terminalia chebula* was found to be cytotoxic against MCF-7 cell lines, and was able to induce apoptosis in MCF7 cell lines. MCF-7 cell lines were 86% inhibited at 320 µg/mL concentration (Pruhtvish et al., 2022). Isolation, characterization of its phytoconstituents, and *in vivo* studies of its anti-breast cancer properties require further perspectives.

3. Discussion

Breast cancer is a major public health problem worldwide. Nonetheless, large geographic variation across countries and world regions exists, with incidence rates ranging from <40 per 100,000 females in some Asian and African countries, to over 80 per 100,000 in Australia/New Zealand, Northern America, and parts of Europe (Arnold et al., 2022). Different patterns and trends have been observed in transitioning countries in South America, Africa, and Asia, where breast cancer incidence is historically low but has been rising rapidly in past decades (Arnold et al., 2022). Evidence from sub-Saharan Africa shows that incidence rates have increased by more than 5% every year in Malawi, Nigeria, and the Seychelles. This is further witnessed by 3–4% per year in South Africa and Zimbabwe (Arnold et al., 2022).

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According to Egue et al. (2019), breast cancer is the most common cancer of all cancers in women for the period 2014-2016 in Cotonou, capital of the Republic of Benin with an age standardized rate (ASR) of 22.6 per 100,000 (Egue et al., 2019).

Nevertheless, breast cancer treatment is extremely expensive, especially for patients in low-incomes countries. Health insurance does not exist in some countries. Diallo et al. (2022) estimated the average cost for the treatment of breast cancer in Senegal at $33713,43 for a period of 31 months. Hence, apart from the side effects of the conventional treatments of breast cancer, patients in low-income countries are confronted with financial burden. It has therefore been observed that majority of breast cancer patients in Africa use medicinal herbs as self-medication or turn to traditional-practitioners to offset the exorbitant cost of breast cancer treatment.

Furthermore, many chemotherapeutic drugs in use today have serious side effects. Targeted therapies can limit some side effects, but there are cancers that do not respond well to the current treatments available. There are also treatments that become ineffective with pro-longed use. The side effects and sometimes ineffectiveness of current treatments indicate the need for novel therapies that are effective against breast cancer. Therefore, it is necessary to investigate for better ways. Botanical mixtures can be an alternative to overcome the limitations of the conventional treatment.

Thus, the use of phytotherapy in 'modern medicine' is a promising approach to alleviate the cost of treatments of breast cancer and bring new plant-derived substances to market. Herbal preparations are to be included in the treatment of breast cancer in the same way as the conventional treatment.

Conclusion

Phytotherapy is employed as a complementary treatment alongside conventional medicine for breast cancer. Although several studies have demonstrated the potential anti-breast cancer activities of various medicinal plants, there is still a lack of research focused on their use as drugs in breast cancer treatment. Limited efforts have been made to explore their full therapeutic potential in clinical settings. Therefore, it is essential to invest in novel and improved clinical trials and studies that adhere to rigorous standards in the 21st century. These efforts should also incorporate traditional medicine practices from different regions, leveraging their empirical knowledge and historical data. By doing so, the discovery and development of new phytomedicines can be accelerated.

Herbal-based and plant-derived products are essential for the treatment of breast cancer and should be further explored for their potential therapeutic applications.

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