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In vitro studies of Asian medicinal plants with potential activity against breast cancer

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ABSTRACT

Breast cancer is the most common cause of cancer in women, and the side effects reported for conventional treatments have motivated scientists to investigate the anticancer properties of natural products such as medicinal plants. This review summarizes the *in vitro* studies on medicinal plants available in Asian countries, including *Aloe vera, Alpinia galangal*, *Centella asiatica, Andrographis paniculata, Curcuma longa, Morinda citrifolia*, *Trigonella foenum-graecum*, *Zingiber officinale*, *Pereskia bleo,* and *Typhonium flagelliforme* that have exhibited potential therapeutic properties against breast cancer. The mechanisms of action and potential drug-natural product interactions are discussed because these plants are commonly used in Asian populations. Clinical trials are warranted to further explore the safety and efficacy of these plants to better manage breast cancer in the future.

1. INTRODUCTION

Based on statistics from 2016, breast cancer is the most common cancer among women in the United States, making up 29% of all newly diagnosed cancers in that year alone. It is also the second most common cause of cancer-related deaths, after lung and bronchial cancers [1]. Depending on the stage of breast cancer, hormone receptor levels or function and the patient's general health, surgery (e.g., lumpectomy or mastectomy), radiation therapy, hormone or endocrine therapy using tamoxifen or aromatase inhibitors, chemotherapy, and targeted therapy are currently the most common anticancer treatments provided [2].

There are serious side effects associated with each treatment which led an interest among scientists to increasingly investigate the potential anticancer effects of natural products including medicinal plants. A study has shown that 30–50% of breast cancer patients have continuous pain in the area of their breast and in their arm and shoulder 3–5 years after undergoing surgery and radiotherapy. Furthermore, 15–25% of these patients have lymphedema, and another 35% have claimed to have shoulder and arm movement limitations [3]. The administration of tamoxifen as a standard endocrine therapy has increased the risks of endometrial carcinoma, thromboembolism, and tamoxifen resistance due to its antiestrogenic effects [4]. In addition, tamoxifen causes vaginal bleeding, discharge or dryness, and hot flushes resulting from its antiestrogenic effects. Aromatase inhibitors, on the other hand, have been shown to increase the risks of bone fractures compared with the effects of tamoxifen because estrogen has a protective effect against osteoporosis [5].

Information on the natural products discussed in this review was obtained by searching the PubMed, ISI Web of Science, and Google Scholar databases using different terms, which include the keywords "natural products," "breast cancer," "Asia," and "Malaysia" combined with the Boolean operators "AND" and "OR." There were no language or search-year restrictions. Based on the search, several medicinal plants that have been shown to have potential beneficial therapeutic effects against breast cancer in Asian countries such as *Aloe vera, Alpinia galangal*, *Centella asiatica, Andrographis paniculata, Curcuma longa, Morinda citrifolia, Trigonella foenum-graecum, Zingiber officinale, Pereskia bleo,* and *Typhonium flagelliforme* are reviewed.

2. *A. VERA*

A. vera, or *Aloe barbadensis* (Miller), which is a member of the Liliaceae family, has been shown to have curative or healing effects. *A. vera* extract exhibits important biological activities including anticancer, antioxidant, immunoprotective, hypoglycemic, hypolipidemic, and antifungal properties [6-9]. *A. vera* exhibits antineoplastic effects by inducing apoptosis and modulating the expression of effector molecules such as down-regulating cyclin D1, CYP 1A1, and CYP 1A2, and up-regulating Bax and p21 expression, in breast cancer

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cells [10]. *A. vera* leaf extract has been shown to exhibit significant inhibitory effect on breast cancer cells by changing the antioxidant and detoxification enzyme activity levels [11].

3. *A. GALANGAL*

A. galangal, known locally as "galangal" or "lengkuas," is commonly used in Southeast Asian countries including Malaysia, Thailand, and Indonesia. For centuries, the rhizome of this plant has been commonly used as food flavoring and medication. Traditional medical practices such as Ayurveda, Unani, Chinese, and Thai folk medicine have used *A. galangal* as a part of their medical system [12]. The active compound in galangal, identified as [E]-8 beta, 17-epoxylabd-12-ene-15, 16-dial [1], and also known as dipertine-1, has been reported to possess antifungal [13] and antitumor activities [14,15]. *A. galangal* extract possesses bioactive compounds such as flavonoids (kaempferol, kaempferide, and galangin), terpenoids (10-acetoxychavicol acetate, 10-acetoxy eugenol, galanal A, galanal B, and galanolactone), and phenolic acids. These compounds have been demonstrated to have proapoptotic effects and to inhibit the proliferation of a breast cancer-derived cell line [16]. However, it has been found that *A. galangal* extract from Malaysia is less cytotoxic toward MCF7 breast cancer cell line than *A. galangal* extract originating from Thailand [17]. It is plausible that this difference in cytotoxicity is due to the higher levels of 1'-acetoxychavicol acetate in the sample from Thailand, which could be a result of ecological variations and differences in the times of collection [18].

4. *C. ASIATICA*

C. asiatica, which is locally known as "pegaga" and found in wet areas in many Asian countries, is one of the common plants traditionally used for treating several types of ailments. *C. asiatica* is a medicinal plant that contains triterpene glycosides such as centellasaponin, asiaticoside, sceffoleoside, and madecassoside [19], as well as terpenoids such as madecassic and asiatic acids [20,21]. A study on the effect of *C. asiatica* on breast cancer cells indicated the presence of apoptosis as shown by nuclear condensation, increased annexin staining, loss of mitochondrial membrane potential, and induction of DNA breaks [22]. Moreover, the presence of phenolic and flavonoid constituents in *C. asiatica* extract suggests antioxidant activities and potential antitumor effects against breast cancer [23,24]. The combined use of asiaticoside and the chemotherapeutic agent vincristine on MCF-7 and its ADM-resistant line (MCF-7/ADM) cells has been shown to have a synergistic effect, inducing apoptosis and increasing the antitumor activity of vincristine in cancer cells compared with asiaticoside alone and vincristine alone which provides useful information for developing new cancer chemotherapies [25].

5. *A. PANICULATA*

A. paniculata is an important herbal medicine that has been used for centuries in many Asian countries including India, China, Thailand, and Malaysia. The plant is found in moist and shady areas. Locally, it is known as "hempedu bumi." The leaves and stems (the parts most often used) have been reported to contain diterpenes, flavonoids, and stigmasterol [26]. The anticancer activity of the dichloromethane fraction of *A. paniculata* methanolic extract has been reported [27]. Andrographolide is a natural diterpenoid lactone isolated from *A. paniculata*, and it shows inhibitory effects, by causing cell cycle arrest during the G0/G1 phases, inducing cell cycle inhibitory protein p27 expression and reducing the expression of cyclin-dependent kinase 4 in breast cancer cell lines [28]. Benzylidence, a derivative of andrographolide also has been reported to show its inhibitory effects by inducing of G1 arrest and apoptosis in cancer cells [29]. Hypoxia is common in breast cancer and results from the tumor outgrowing and the ability of the existing vasculature to supply the tissue with oxygen [30]. To adapt this hypoxic environment, the levels of hypoxia-inducible factors are increased, leading to the induction of angiogenesis, cell proliferation, invasion, and metastasis [31]. Andrographolide is able to inhibit hypoxia-inducible factor-1 expression in breast cancer cell lines, highlighting the potential effects of andrographolide in treating breast cancer [32]. *A. paniculata* can induce DNA fragmentation and increase the frequency of apoptosis in human breast cancer cell lines in both time- and concentration-dependent manners through increased p53 Bax and caspase-3 expression, and reduced bcl2 expression [33].

6. *C. LONGA*

C. longa is a well-known tropical herb, which grows abundantly in Asia and is locally known as "turmeric" or "kunyit" in Malaysia. It is commonly used in cooking to flavor foods and to give color to dishes due to its rich yellow color, and it is occasionally eaten raw. Curcumin, the active ingredient in turmeric, is found in the plant's rhizome. Curcumin has been shown to promote cell cycle arrest and apoptosis at the G2/M phase of cell proliferation by inhibiting the dynamic assembly of microtubules through mitotic checkpoint activation in MCF-7 cells [34]. Curcumin inhibits Ki-67 expression and increases levels of proliferating cell nuclear antigen and p53 mRNAs in breast cancer cells [35]. It also inhibits β-catenin, cyclin D1, and Slug expression in MDA-MB-231 and MCF-7 cells, suggesting that it may inhibit the abnormal activation of the Wnt/β-catenin signaling pathway that is commonly associated with breast cancer. Curcumin also inhibits MCF-7 cell adhesion and invasion by down-regulating urokinase-type plasminogen activator protein expression through NF-κB activation [36].

7. *M. CITRIFOLIA*

M. citrifolia is a plant commonly found in Southeast Asia, especially in Malaysia. Much research has been conducted to investigate the health benefits of all parts of the plant, including the fruits (called "noni fruit"), leaves, bark and roots, which have been shown to contain several active compounds with high medicinal value. Its fruit juice inhibits proliferation, increases apoptotic cell cycle arrest, reduces intracellular generation of reactive oxygen species, and ameliorates mitochondrial membrane potentials in MCF-7 and MDA-MB-231 breast cancer cell lines [37]. It also inhibits aromatase enzyme, indicating its potential in the treatment of breast cancer [38].

8. *T. FOENUM-GRAECUM*

T. foenum-graecum, which is primarily produced in India, is extensively used in the traditional Indian medical system for treating various diseases. This herb is also used in Malaysia as a spice for culinary purposes [39]. Its seeds, locally known as "fenugreek" or "halba," have been reported to possess antibacterial, galactagogue, and carminative properties. *T. foenum-graecum* induces apoptosis in MCF-7 human breast cells [40,41] but not in normal cells [42,43].

9. *Z. OFFICINALE*

Z. officinale is used worldwide as flavoring agent and spice, and is locally known as "ginger" or "halia." The chemical [6]-gingerol

(1-[4'-hydroxy-3'methoxyphenyl]-5-hydroxy-3-decanone) found in its rhizome is a pungent phenolic ingredient that possesses anti-inflammatory, antihepatotoxic, and anticardiotoxic effects, as well as antioxidant properties [44]. Cell adhesion, invasion, motility, and metastasis have been shown to be inhibited by [6]-gingerol in human breast cancer cell lines [45]. In addition, the proliferative and colony-forming abilities of breast cancer cell lines are suppressed by [6]-gingerol. Apoptosis, loss of cell viability, chromatin condensation, DNA fragmentation, caspase 3 activation, and poly (ADP-ribose) polymerase cleavage have also been found following [6]-gingerol treatment [46]. Furthermore, it inhibits proliferation in breast cancer lines without affecting normal mammary epithelial cell lines [47], indicating its safety in humans.

10. *P. BLEO*

P. bleo has been traditionally used for medicinal purposes in Asian countries including Malaysia. It is also known as "jarum tujuh bilah" and belongs to the Cactaceae family. This plant is believed to treat various diseases such as cancer, rheumatic conditions, ulcers, diabetes, and hypertension. Methanolic extracts from the combined stems and leaves of *P. bleo* contain several bioactive compounds that can cause apoptosis in breast cancer cells through the activation of caspase-3 and c-myc pathways [48]. In addition to their cytotoxic activities against MCF 7 breast cancer cell lines, the leaves of the plant (both crude methanolic extracts and ethyl acetate fractions) do not exhibit any cytotoxicity to normal human fibroblast cell lines [49]. The plant also contains Vitamin E (α-tocopherol), which has antioxidant [50], antiproliferative, and anticancer properties [51], making it a useful herb that should be further investigated in controlled clinical trials as a possible therapeutic agent against breast cancer. However, the plant's leaves (methanolic and aqueous extracts) and stem (crude methanolic and fractionated ethyl acetate, *t*-butanol, and aqueous extracts) do not show any significant antiproliferative effects against the murine mammary cancer (4T1) and normal murine fibroblast (NIH/3T3) cell lines [51,52]. The inconsistency of these findings may be due to the use of different cell lines and plant parts (stem and leaves) which may contain different bioactive compounds. Therefore, additional studies on the effectiveness of *P. bleo* against breast cancer cells should be investigated due to its potential anticancer property.

11. *T. FLAGELLIFORME*

T. flagelliforme is commonly known as "Keladi Tikus" or "Rodent Tuber" by Malaysians. The tuber of the plant has been traditionally used to treat cancer. Several studies have confirmed its antioxidant and pain-relieving property, and its potential to prevent metastasis in various types of cancer cells such as breast, cervical, nasopharyngeal, prostate, pancreatic, and lung cancer lines [53,54]. The tuber contains an active protein called lectin, which has anticancer and antiproliferative properties. This may be due to the difference in the sugar component of the glycoproteins on the surface of cancer cells relative to those on normal cells, which may result in different effects of lectin at the cell surface [55]. The tuber of *T. flagelliforme* has been found to have a stronger cytotoxic effect on breast cancer cell than on cervical cancer cells [56].

These medicinal plants, which are available in Asian countries, as well as their active compounds and mechanisms of action against breast cancer, are summarized in Table 1.

12. ADVERSE EFFECTS AND DRUG-NATURAL PRODUCT INTERACTIONS

Natural products have always been assumed or believed to be safe because they are "natural." However, this assumption is not necessarily valid because many modern therapies are synthesized from natural products or contain chemicals that are structurally similar to those derived from natural products including medicinal plants. In addition, many natural products are not rigorously tested in standardized clinical trials compared with how modern or conventional medications are evaluated [57]. Some problems may also emerge when using natural products together with chemotherapeutic agents because of the likelihood of a drug-natural product interaction. For example, increased skin sensitivity toward radiation therapy, irregular blood pressure, and problems with anesthetic agents used during surgery have been reported when drugs and natural products have been used together [58].

Bajwa and Panda [59] have reported on several plants that can be a significant concern to anesthesiologists, for example, products derived from *Echinacea purpurea, Ephedra vulgaris, Allium sativum, Ginkgo biloba,* Ginseng*, Valerian officinalis, Z. officinale, Tinospora cordifolia,* and *C. longa*. Furthermore, many plant metabolites have not been fully investigated, and they can potentially act as carcinogens and may disturb cellular metabolic processes in the body [60].

There is a chance of herb-drug interactions between the various active constituents of *A. vera* and other drugs in patients who are simultaneously prescribed several medications. For example, prostaglandin synthesis may decrease, which can result in the secondary aggregation of platelets [61]. In a case report, a 35-year-old woman lost 5 L of blood during surgery for hemangioma following *A. vera* consumption (4 tablets/day for 2 weeks before admission), which was suspected to be caused by an interaction between *A. vera* and sevoflurane [62]. Another patient presented with severe acute hepatitis following *A. vera* consumption. The woman, who had consumed *A. vera* tablet (500 mg) approximately for 4 weeks before being admitted to the hospital, presented with progressive jaundice, pruritus, alcoholic bowel movements, and abdominal discomfort [63], indicating that additional studies should be conducted on *A. vera*-drug interactions. Regardless of its wound-healing and emollient properties, *A. vera* has also been shown to cause contact dermatitis, photodermatitis, and erythema after topical applications of *A. vera* gel [64-66]. Oral consumption of *A. vera* may cause serious side effects such as diarrhea, hepatitis, laxative-dependency or worsening of constipation, abdominal cramps, and the production of red urine [66].

A. galangal has been reported to be a safe plant because no toxicity has been reported when orally administered to mammals up to the dose of 300 g/kg [67]. *C. asiatica* has been shown not to cause any toxicity when administered orally if consumed at recommended doses. However, when applied externally, burning sensations and skin allergies have been reported in addition to headache, nausea, dizziness, stomach upset, and serious drowsiness that tend to occur at high doses [68]. Patients who take medications that can cause reductions in sleep or anxiety are advised to avoid this herb as it causes sedation at high dose [69,70], however, to date, no reports are available regarding its interaction with those medications.

A. paniculata has also been reported to be a safe medicinal plant. A study was conducted to investigate potential toxic effects of dried *A. paniculata* extract on the testis of male Sprague Dawley rats over

Table 1: Medicinal plants from Asian countries with potential activity against breast cancer.

Medicinal plants	Mechanism of actions	Models	References
A vera	Induction of apoptosis and modulation of the expression of effector molecules in tumor cells	Human breast carcinoma cell lines (MCF-7)	[10]
A galanga	Antiproliferative activity and apoptosis induction	MCF-7 cell lines	[16]
	Cytotoxicity effects	MCF-7 cell lines	[17]
C asiatica	Apoptosis promotion	MCF-7 cells lines	[22]
	Antioxidant effects and antitumor potential	Human breast cancer cell line (MDA MB-231)	[23,24]
A paniculata	Induction of DNA fragmentation and apoptosis promotion Induction of G1 arrest and apoptosis in cancer cells Blockage of the cell cycle at the G0-G1 phase through the induction of the cell cycle inhibitor p27 and a concomitant decrease in Cdk4 levels	TD-47 human breast cancer cell lines MCF-7 cells lines MCF-7 cell lines	[33] [29] [28]
C longa	Inhibition on the expression of Ki-67, proliferation of cell nuclear antigen, and p53 mRNAs	Breast carcinoma cell lines	[35]
M citrofolia	Inhibition of proliferation, increased apoptosis, cell cycle arrest, and reductions in the intracellular generation of reactive oxygen species and the amelioration of mitochondrial membrane potential	MCF-7, MDA-MB-231 breast cancer cell lines	[37]
T foenum	Apoptosis induction and the inhibition of cell proliferation	MCF-7 cell lines	[40,41]
Z officinale	Proliferation inhibition and apoptotic cell death	Human breast cancer cell lines (MCF-7 and MDA-MB-231)	[46,47]
P bleo	Apoptosis of breast cancer cells	Breast carcinoma T47-D cell lines	[48]
T. flagelliforme	Antiproliferative and cytotoxic effects.	MCF-7 cell lines.	[55,56]

A. vera: Aloe vera, A. galangal: Alpinia galangal, C. asiatica: Centella asiatica, A. paniculata: Andrographis paniculata, C. longa: Curcuma longa, M. citrifolia: Morinda citrifolia, T. foenum: Trigonella foenum-graecum, Z. officinale: Zingiber officinale, P. bleo: Pereskia bleo, T. flagelliforme: Typhonium flagelliforme.

60 days. No subchronic testicular toxicity was detected following its administration at doses of 20, 200, or 100 mg/kg [43]. In addition, the adverse effects reported in clinical trials are moderate, occasional, and short term, which include fatigue, allergic reactions, headaches, lymph node pain, lymphadenopathies, diarrhea, nausea, and metallic tastes [71].

C. longa has been extensively used for medicinal purposes, administered either topically, orally, or through inhalation. Curcumin at doses of 800–2500 mg/day for 3 months is safe in a human trial [72]. Furthermore, turmeric at 2.25 g/kg and alcoholic turmeric extract at 300 mg/kg do not cause adverse effects on liver, kidney, and heart [73].

A study conducted on human subjects who consumed 750 mL/day of *M. citrifolia* juice for 28 days is found to have no toxic effects on major organs including liver [74]. Nevertheless, some adverse events such as a headache, coughing, nausea, menstrual cramps, nasal discharge, stomachache, toothache, sore throat, vomiting, increased bowel movements, as well as upper respiratory and urinary tract infections were observed in subjects who consumed the fruit juice [75,76].

Z. officinale may show some antiplatelet effects [77], and therefore, patients who take heparin, aspirin, and related agents should avoid any products containing this herb. However, a study conducted on rats administered *T. foenum-graecum* modified diet (5, 10, and 20%) for 90 days showed that they had comparable hematological parameters, histological findings, liver function, and feed efficiency ratios when compared with animals in control group [78]. *T. foenum-graecum* is also non-toxic to fibroblast cells at a dose of up to 100,000 ng/mL and therefore has the potential for being useful in treating breast cancer [55].

P. bleo up to the doses of 2500 mg/kg does not cause significant changes in behavior such as ataxia, hyperactivity, or hypoactivity in mice after a 2-week observation period. It increases body weight, but no toxicity is observed in the mice [79]. Moreover, *P. bleo* extract does not have cytotoxic effect on normal MRC-5 cells [80].

13. CHALLENGES, FUTURE PERSPECTIVES, AND CONCLUSION

Many challenges exist when utilizing plants in treating breast cancer. Variations in the geographical location of the plants and the time they are collected increase the variability in the findings of studies on these products, making the comparison of data from across the globe challenging. The utilization of different plant parts (roots, stems, fruits, and leaves) further increases the variability of the data obtained.

The use of medicinal plants as adjuvants remains an approach that could have vast potential for providing additional treatment options, and this potential should be explored in the future. In addition, new technologies that can combine chemistry with high-throughput screening may help facilitate the production of new synthetic drugs that are based on plants and that can act as templates for the production of novel-targeted compounds. The advancement of technologies, including those that can aid in the identification of new genes involved in the reaction to these compounds in performing gene expression studies, may help facilitate this process.

Overall, although the use of medicinal plants as anticancer agents has shown good potential, not only in the Western countries but also in Asian countries, data from controlled clinical trials in humans are still lacking. Since not all natural products including plants should be assumed to be safe, more scientific investigations, which examine appropriate dosing, product efficacy, and their adverse effects, should be conducted. This will allow informed decisions to be made by the patients and medical practitioners.

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