Clinics in Surgery

Review Article
Published: 27 Jan, 2021

Plant-Based Natural Products for Breast Cancer Prevention: A South Asian Association for Regional Cooperation (SAARC) Countries Perspective

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Abstract

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer-related deaths among women worldwide. Chemotherapeutic drugs have yielded limited anticancer activity and have not reduced the high recurrence rate. This has fueled efforts into the identification of more effective anticancer agents. A focus on natural products with potential anticancer activity exhibiting less adverse effects has led to the study of medicinal plants. This has resulted in the discovery of compounds with remarkable chemical structures exhibiting diverse biological activities. Geography and climate variations between the South Asian Association for Regional Cooperation (SAARC) countries have provided an array of environmental conditions that yield versatile plant species. These may be used for the preparation of traditional medicine and have attracted significant attention from the scientific community. In this review, we focus on the anticancer properties of twenty-five medicinal plant species and their active constituents, which grow in SAARC countries including India, Bangladesh, Pakistan, Nepal, Sri Lanka, Bhutan, the Maldives, and Afghanistan. The mechanisms of action associated with these compounds provide a glimpse of the current trends driving anticancer drug discovery, especially with respect to breast cancer.

Keywords: Plant; Breast cancer; Prevention; South Asian Association for Regional Cooperation (SAARC)

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Received Date: *09 Dec 2020*
Accepted Date: *21 Jan 2021*
Published Date: *27 Jan 2021*

Citation:
Alam B, Javed A, Fanar A, Choi H-J, Lee S-H. Plant-Based Natural Products for Breast Cancer Prevention: A South Asian Association for Regional Cooperation (SAARC) Countries Perspective. Clin Surg. 2021; 6: 3047.

Introduction

Cancer is a significant healthcare issue that affects two-thirds of the global population and is the second most common cause of death worldwide. Only modest progress has been made in reducing the morbidity and mortality of this group of diseases [1]. Breast cancer is the most common cancer in women, both in developing and developed countries. According to the GLOBOCAN estimate, more than half (52.9%) of the 1.67 million new breast cancer cases were diagnosed in developing countries in 2012, whereas the corresponding figure in 1980 was only 35% [2]. In South Asia, approximately 588 million women over the age of 15 are experiencing a growing breast cancer epidemic [3]. In 2012, an estimated 200,000 new breast cancer cases have occurred in South Asia and approximately 975,000 women have died of this disease [2]. Despite current efforts to promote health, an increased lifespan in developing countries resulting from efficient management of infectious diseases and increased adaptation of a Western lifestyle are considered risk factors for breast cancer [4]. Chemoprevention, by definition, is a means of controlling cancer by administering one or more naturally occurring and/or synthetic agents to entirely prevent, slow, or reverse cancer occurrence or its development. This concept has gained increased attention, in part, because of its cost-effectiveness. An increased understanding of the epigenetic, genetic, molecular, cellular, and developmental characteristics of cancer has created opportunities to disrupt and reverse the initiation and progression of this disease. Additionally, these advances have identified physiological and pharmacologic mechanisms for therapeutic intervention aimed at preventing end-stage, invasive disease or delaying cancer development [5].

According to the WHO, more than 80% of the world's population depends on traditional medicine for their primary healthcare needs [6]. Plants represent a rich source of medicinal compounds and more than half of the currently available drugs are natural compounds or derivatives of such compounds. Over 60% of the currently used anticancer agents are derived from natural sources [7]. The anticancer effects of these natural products target inflammatory processes and

oncogenic transformation, including alterations in cell cycle control, apoptosis evasion, angiogenesis, and metastasis [8].

Geography and climate variations among the South Asian Association for Regional Cooperation (SAARC) countries provides a plethora of environmental conditions for the growth of versatile plant species that may be used for the preparation of traditional medicines and has drawn significant interest from the scientific community. In this review, we focus on the anticancer potential of medicinal plant species and their active constituents, particularly against breast cancer, which are commonly grown in SAARC countries including India, Bangladesh, Pakistan, Nepal, Sri Lanka, Bhutan, the Maldives, and Afghanistan.

Breast Cancer and Its Signaling Pathways

Breast cancer is hallmarked by the uncontrolled growth of cells to form a solid lump or tumor in the lobules (milk-producing glands) or ducts (the passages that carry milk to the nipples) of breast tissue. These cells may start disseminating into the blood and lymphatic systems even at early stages or when the tumor size is small [9].

The underlying mechanisms associated with individual breast cancer subtypes are complex and their corresponding gene expression profiles are dependent on various oncogenic pathways. The maintenance and differentiation of normal breast tissue are controlled by signaling pathways that involve cytokines, chemokines, growth factors, steroid hormones, adhesion molecules, and their associated receptors. Attenuation of these pathways by single or multiple components of the tumor microenvironment has been implicated in the promotion, growth invasion, and metastasis of breast cancer [10]. Advances in our understanding of the etiology, biology, and signaling systems involved in the development and survival of breast cancer have identified putative targets that may be exploited in the development of new agents for breast cancer treatment.

The epidermal growth factor receptor (EGFR or HER-2) family consists of cell surface tyrosine kinase receptors that are involved in the regulation of cell proliferation, differentiation, and survival in breast cancer. Each HER receptor contains an extracellular domain involved in ligand binding and an intracellular domain that exhibits tyrosine kinase activity. Upon ligand binding, the extracellular domain of the receptors undergoes a conformational change resulting in the phosphorylation of the intracellular tyrosine kinase domain. This leads to the activation of multiple signaling pathways that promote proliferation and survival, including the PI3K/Akt/mTOR, Erk1/2MAPK, and JAK/STAT pathways [11,12]. A similar scenario occurs for HER2 in which activation occurs in a ligand-independent manner, predominantly when the receptor is overexpressed or mutated [13]. Constitutive activation of growth factor signaling pathways resulting from the overexpression of HER2 serves as an oncogenic driver in breast cancer. Herceptin, also known as trastuzumab, is a humanized recombinant monoclonal antibody that attaches to the extracellular domain of HER2 and ultimately exerts a selective antitumor effect. For over a decade, the drug has dramatically altered the response rate and progression-free survival of metastatic diseases including breast cancer. Trastuzumab in combination with other drugs (i.e. lapatinib, pertuzumab) or chemotherapy for metastatic cancer improves overall survival and attenuates disease recurrence and death when administered in an adjuvant setting, which is the basis for systemic treatment of HER2-overexpressing tumors [14,15]. The drug not only inhibits HER2 signaling pathways, but is active against HER2-overexpressing cells that stimulate immune-mediated responses. In addition, trastuzumab also induces anti-angiogenic effects and attenuates the proapoptotic threshold for chemotherapy [16]. Trastuzumab, in combination with various chemotherapeutic drugs, has been evaluated in xenograft models and HER2-overexpressing cell lines. A synergistic or additive interaction for epirubic, docetaxel, doxorubicin, and gemcitabine were observed [15,17]. As a consequence, trastuzumab demonstrated superior clinical results for all stages in HER2-positive breast cancer patients.

The *Rous sarcoma virus* (v-Src) tyrosine kinase functions as a hub for a vast array of signal transduction pathways, including the Platelet-Derived Growth Factor Receptor (PDGFR), EGFR, and Insulin-like Growth Factor-1 Receptor (IGF-1R) pathways, to influence cell proliferation, differentiation, motility, and breast cancer survival [18]. Heat Shock Protein 90 (HSP90) is required for the stability and function of several inherently unstable candidate signaling proteins, such as Akt, HER2, Bcr-Abl, c-Kit, EGFR, and PDGFR-α. HSP90 maintains these proteins poised for activation until they are stabilized by conformational changes associated with the formation of signal transduction complexes [19]. In addition, activation of Poly (ADP-ribose) Polymerase 1 (PARP-1), a family of enzymes largely associated with the maintenance of genomic stability, is a component of the immediate cellular response to DNA strand breaks, converting them into an intracellular signal through the poly (ADP-Ribosylation) of nuclear proteins [20]. Several studies have shown that PARP is overexpressed in breast cancer along with the negative estrogen receptor, progesterone receptor, and HER2. BRCA1 and BRCA2 dysfunction is associated with the inhibition of PARP enzymatic activity, resulting in cell cycle arrest and subsequent apoptosis [21].

Angiogenesis is a complex and dynamic process that is essential for tumor development into detectable localized masses and for metastasis. It is regulated by a variety of pro- and anti-angiogenic molecules, such as the VEGF and PDGF protein families and their receptors (VEGFR-1, VEGFR-2, VEGFR-3, PDGFR- α, and PDGFR-β) [22]. Activation of VEGFRs and PDGFRs initiates signaling that plays a central role in angiogenesis and growth. These two signaling pathways represent important targets for breast cancer therapy. Likewise, estrogen along with its receptor stimulate various physiological functions in mammals and are associated with the progression and development of various ailments including cancers (i.e. ovarian, colorectal, breast and endometrial), CVD, and neurodegenerative diseases. Thus far, two Estrogen Receptor (ER) genes have been identified in mammals (i.e. ERα and Erβ) which exhibit similar ligand and DNA-binding features, but distinct function and tissue distribution [23]. Estrogen binds to the ER after entering the cell, separates from heat shock proteins, and undergoes phosphorylation, conformational changes, and dimerization before binding to estrogen response elements. In breast cancer, tamoxifen stimulates cell growth *in vitro*. Tamoxifen exhibits little affinity for the ER. It is transformed in the liver by cytochrome P450 CY3A4 and CYP26 isoforms into N-desmethyl-4-hydroxy tamoxifen and 4-hydroxy tamoxifen, and shows more efficiency in binding with the ER compared with the parental drug. After attachment, co-repressor proteins (i.e. SMRT and NCoR) regulate various gene functions. The complex requires PAX2 to induce anticancer effects as a result of the suppression of the pro-proliferative protein, ERBB2. It has been reported that high daily doses of tamoxifen result in the suppression of cancer. However, 80% of the animals in a trial showed no signs

Table 1: Summary of the anticancer activities of selected plants found in SAARC countries.

Plant (Family)	Ethnopharmacological relevance	Mechanism of action	Reference
Abrus precatorius L. (Leguminosae)	Erectile dysfunction, antifertility, malaria, eye disease, jaundice, asthma, gastritis, abortion, gonorrhea and snakebite	Cytotoxicity, p21- and p53-induced apoptosis, growth inhibition	[26,27]
Acrostichum aureum L. (Ptridiaceae)	Rheumatism, wounds and boils and blood clotting	Cytotoxicity and apoptosis	[28-30]
Aegiceras corniculatum L. (Myrsinaceae)	Fish poisoning, asthma, diabetes, rheumatism and inflammation	Cytotoxicity, G2/M cell cycle arrest, altered mitochondrial membrane potential, induced apoptosis	[28,31]
Aegle marmelos (*L.*) Correa. (Rutaceae)	Diarrhea, dysentery heart disorders, ulcers, diabetes, dyspepsia, cholera, jaundice, and fish poisoning	Cytotoxicity, activation of tumor necrosis factor-a (TNF-a), TNF receptor-associated death domain, and caspases	[32-34]
Alangium salvifolium Wang (Alangiaceae)	Diarrhea, paralysis, piles, vomiting, snakebite, and constipation	Cytotoxicity, growth inhibition	[35,36]
Amoora rohituka Roxb. (Meliaceae)	Cancer, tumors, spleen, and liver disease and rheumatism	Cytotoxicity, cell cycle arrest at G2/M phase, caspase-activated apoptosis, growth inhibition	[37-39]
Artocarpus heterophyllus Lam. (Moraceae)	Diarrhea, fever, ulcers, antisyphilic, wound healing, anemia, cough, asthma, and dermatitis	Cytotoxicity, caspase-3, and -8 induced apoptosis	[40,41]
Blumea lacera L. (Asteraceae)	Astringent, stimulant, anthelmintic, diuretic, cough, bronchitis, dysentery, wound healing, and cholera	Cytotoxicity, reactive oxygen species-induced cytotoxicity	[42-44]
Bruguiera gymnorrhizais L. (Rhizophoraceae)	Diarrhea, astringent, blood clotting, and blood pressure	Cytotoxicity, induced apoptosis through reduction in mRNA levels of Bcl-2, and hTERT	[28,45]
Daucus carota L. (Apiaceae)	Dysentery, leprosy, piles, asthma, jaundice, bronchitis, diarrhea, inflammation, kidney disorders, cardiotonic and menstrual diseases	Caspase-3-dependent apoptosis, Bcl-2 down regulation, Bax up-regulation, inhibition of ERK pathway, cell cycle arrest	[46,47]
Dillenia indica L. (Dilleniaceae)	Expectorant, laxative, tonic, abdominal pain, astringent, antifungal, antibacterial and diarrhea	Cytotoxicity, induced apoptosis via down regulation of Sp1, cell cycle arrest at G2/M by the phosphorylation of cdc2	[48,49]
Embelia ribes Burm. F. (Myrsinaceae)	Skin diseases, contraceptive, dental caries, diuretic, vomiting, bloating, indigestion, gastritis, and constipation	Cytotoxicity, cell cycle arrest at in sub-G1 phase, apoptosis induction by down regulation of Bcl-2, Bcl-xL, survivin, IAP- 1, IAP-2, and cyclin D1, caspase-3 activation	[31,50]
Lantana camara L. (Verbenaceae)	Diaphoretic, tonic epilepsy, gastropathy, dysentery, wounds, ulcers, swellings, fever, eczema, and rheumatism	Cytotoxicity, cell cycle arrest at the G0/G1 phase, induced apoptosis by activating caspase-3 via the down- and up-regulation of Bcl-2 and Bax expression, respectively	[51-53]
Murraya koenigii Linn. (Rutaceae)	Stimulant, dysentery, diabetes, tonic, stomachic and carminative, cooling, piles, thirst, inflammation, and itching and blood disorders	Growth inhibition, intrinsic and extrinsic apoptosis, G0/G1-phase arrest, up-regulation of p53 as well as p27 and p21	[54-57]
Nelumbo nucifera Willd. (Nelumbonaceae)	Spermatorrhoea, leucoderma, smallpox, dysentery, epistaxis, cough, hematemesis, fever, hemoptysis, hematuria, cholera, hepatopathy and hyperdipsia	Cell cycle arrest at the G0/G1 phase, ADR-mediated apoptosis and anti-angiogenic response, phosphorylation of cyclin and cdks	[58-60]
Nyctanthes arbor-tristis L. (Oleaceae)	Loss of appetite, piles, liver disorders, biliary disorders, fever, malarial, rheumatism, and diaphoretic	Cytotoxicity, caspase-3-dependent apoptosis	[61-63]
Physalis minima L. (Solanaceae)	Jaundice, angina pectoris, abdominal pain, flatulence, eye disease, asthma, bronchitis, and urinary disorder	Growth inhibition, apoptosis, autophagic cell death associated with c-Myc, p53, and caspase-3 dependent pathway	[64-66]
Polyalthia longifolia Benth. & Hook. f. (Annonaceae)	Fever, skin disease, diabetes, hypertension, and helminthiasis	Cytotoxicity, cell cycle arrest at the sub-G0 phase, induce apoptosis via caspase activation and cleavage of PARP	[67,68]
Pterocarpus santalinus L. f. (Fabaceae)	Vomiting, eye diseases, mental aberrations, ulcers, inflammation, anthelmintic, tonic, hemorrhage, dysentery, and cooling agent	Apoptosis induction, chromatin condensation, DNA fragmentation, Sub-G1 phase cell accumulation	[69]
Solanum nigrum Linn. (Solanaceae)	Pain, inflammation, fever, snakebite, glaucoma, trachoma, cataract, stomach ulcer, and cough	Induction of apoptosis and/or autophagocytosis, JNK activation, proapoptotic factors like Bax, cytochrome c release, activation of caspases	[70-73]

of tumor development at small doses over a longer period which was more beneficial compared with long term administration. Long term tamoxifen therapy is superior and may be combined with an aromatase inhibitor. Also, tamoxifen therapy results in fewer serious side effects, although some breast cancer patients are at risk for coronary heart diseases and osteoporosis [24]. Remarkably, in mammary and breast tissues, tamoxifen exhibited anti-estrogenic effects, yet it lowered circulating cholesterol and estrogen in bone and ameliorated hypercholesterolemia [25]. The average dose of tamoxifen is 20 mg/day which does not pose any side effects in breast cancer patients.

Medicinal Plants with Anticancer Potential from SAARC Countries

Different species of plants (some worldwide, others strictly native) from SAARC countries have been reported to exhibit activity in breast cancer.

Abrus precatorius L

Abrus precatorius L, which is commonly known as "Indian liquorice", belongs to the *Fabaceae* family. Extracts of the *A. precatorius* leaf inhibit MDA-MB-231 cell growth by inducing apoptosis [26]. Moreover, triterpenoids, abruslactone A (i), and abrusogenin (ii), which were isolated from the leaves and stem of *A. precatorius*, exhibit moderate cytotoxicity against MCF-7 breast cancer cells [27].

Acrostichum aureum L

Acrostichum aureum L (*Ptridiaceae* family), locally known as "Tiger fern," is an evergreen shrub distributed widely throughout Bangladesh, India, and Sri Lanka, primarily in mangrove forests and coastal areas. The methanolic extract of *A. aureum* leaves exhibits selective cytotoxicity against MDA-MB-435S cells [28]. Moreover,

(2S,3S)-sulfated pterosin C (III) (iii), patriscabratine (iv), and tetracosane (v) have been isolated from *A. aureum* and have shown selective cytotoxicity against MDA-MB-231 and MCF-7 cells [28-30].

Aegiceras corniculatum L

The mangrove tree or shrub, *Aegiceras corniculatum* (*Myrsinaceae* family), is widely distributed in the coastal and estuarine areas of India, Bangladesh, and Sri Lanka. The aqueous extract of A. corniculatum shows selective cytotoxicity against MDA-MB-435S cells [28]. Phytochemical studies have shown that embelin (vi) induces MCF-7 breast cancer cell apoptosis in a dose- and time-dependent manner, alters cell mitochondrial membrane potential, and blocks the cell cycle at the G2/M phase. Moreover, embelin promotes the mitochondrial release of cytochrome c by regulating Bax and Bcl-2, resulting in the activation of caspase-3 and -9 [31].

Aegle marmelos (L.) Corr.

Aegle marmelos (L.) Corr., commonly known as Bael, is a deciduous tree of the Rutaceae family. It originated in India, but presently grows in most SAARC countries. The hydroalcoholic extract of the *A. marmelos* leaves exhibits an anti-proliferative effect on MCF-7 and MDA-MB-231 cell lines [32]. Skimmiarepin A (vii) and C (viii), compounds isolated from the hydroalcoholic extract, inhibited HIF-1 activation by blocking the hypoxia-induced accumulation of HIF-1α protein through hyperphosphorylation and inactivation of translation initiation factor eIF2α and elongation factor eEF2 in T47D cells [33]. In addition, marmelin (ix) was isolated and characterized from the ethyl acetate fraction of *A. marmelos* and activates apoptosis in epithelial cancer cells through the activation of tumor necrosis factor-α (TNF-α), the TNF receptor-associated death domain, and caspases [34].

Alangium salviifolium Wang.

Alangium salviifolium Wang is locally known as "Ankor Kanta" in Bangladesh, "Angol" in India, and "Ruk anguna" in Sri Lanka. It belongs to the *Alangiaceae* family. Various alkaloids have been isolated from *A. salviifolium* including 10-O-demethylcephaeline (x), which exhibits potent cytotoxic activity against MCF-7 cells [35,36].

Amoora rohituka (Roxb).

Amoora rohituka (Roxb) belongs to the *Meliaceae* family and is locally known as "Royna" in Bangladesh and "Harin-hara" in India. Organic solvent extracts of the *A. rohituka* bark exhibit selective cytotoxicity against MCF-7 cells [37]. Triterpenic acid, or amooranin (xi), identified from the bark of *A. rohituka*, can arrest the cell cycle in the G2/M phase and induce caspase-dependent apoptosis in breast carcinoma. *Amoora rohituka* is also known to be effective against breast cancer, colon cancer, cervical cancer, and leukemia cell lines [38,39].

Artocarpus heterophyllus Lam.

Artocarpus heterophyllus Lam., which belongs to the Moraceae family and is popularly known as jackfruit or the Ceylon Jack tree, is an important tree commonly found in home gardens throughout India, Bangladesh, Nepal, Sri Lanka, and Pakistan. Patel and Patel [40] showed that a methanolic extract from this tree had no activity against MCF-7 cells, however, artocarpin (xii) isolated from the wood of *A. heterophyllus* exhibited potent cytotoxic activity in cultured human T47D breast cancer cells. Mechanistic studies showed that this effect was mediated through the activation of caspase-3 and caspase-8, but not caspase-9 or caspase-10 [41].

Blumea lacera L.

Blumea lacera L. is an annual flowering herb belonging to the Asteraceae family. The methanolic extract of *B. lacera* leaves has shown non-selective cytotoxic activity against MDA-MB-435S cells [42]. Studies have demonstrated that the essential oil in its leaves is responsible for the anticancer effect of *B. lacera*. Specifically, α-humulene acts by reactive oxygen species-induced cytotoxicity and β-caryophyllene potentiates the anticancer activity of α-humulene [43,44].

Bruguiera gymnorrhiza (L.)

Lam.: *Bruguiera gymnorrhizais* (L.) Lam. (Rhizophoraceae family) is commonly known as "Large-leafed orange mangrove." The methanolic extract of the bark as well as different organic soluble fractions of its leaves exhibited antitumor activity in tumor-bearing mice and these fractions were active against the MDA-MB-435S human cancer cell line. Of the several types of phyto-chemicals, Ent-kaurane diterpenoids (ent-16 β-17 α-dihydroxykaurane) (xiii) significantly reduced Bcl-2 protein and mRNA levels, hTERT mRNA levels, and triggered apoptosis in MCF-7 cells [45].

Daucus carota L.

Daucus carota L., commonly known as "carrot," belongs to the *Apiaceae* (Umbelliferae) family and is cultivated in most of the world as a vegetable. Carrot oil extract consists mainly of phenylpropanoids, monoterpenes, sesquiterpenes, and phenol. In addition to polyphenols, which include flavonoids, carrot oil extract significantly increases cell death and decreases cell proliferation in MCF-7 and MDA-MB-231 cell lines through the Erk signaling pathway [46]. β-Carotene (xv) is the main phytochemical of *D. carota*. It arrests the cell cycle at the G2/M phase in MCF-7 cells and at the GO/G1 phase in both MDA-MB-231 and MDA-MB-235 cells. It also induces cytotoxicity through a caspase-dependent apoptosis pathway [47].

Dillenia indica L.

Dillenia indica L. (Dilleniaceae), known as "Elephant apple," grows in the moist and evergreen forests of Bangladesh, India, and Nepal. The methanolic extract of the *D. indica* fruit exhibits significant cytotoxicity against MCF-7 and MDA-MB-231 cells [48]. Betulinic acid (xvi), a pentacyclic triterpenoid isolated from *D. indica* bark, decreased proliferation and induced apoptosis in estrogen receptor-negative MDA-MB-231 breast cancer cells by downregulating Sp1, Sp3, and Sp4 accompanied by increased zinc finger ZBTB10 expression and decreased microRNA-27α levels. The bark extract also induced cell cycle arrest in the G2/M phase and increased Myt-1 mRNA, which causes inhibition at G2/M through cdc2 phosphorylation [49].

Embelia ribes Burm. F.

Embelia ribes Burm. F. (Myrsinaceae) is commonly known as "False black pepper." The methanolic extract of the *E. ribes* fruit exhibited a protective effect against multi-mutagenicity, the molecular basis of cancer, and cyclophosphamide-induced genotoxicity in mice [50]. Embelin (vi), a quinonoid compound of *E. ribes*, induced apoptosis in MCF-7 breast cancer cells in a dose-and time-dependent manner through the induction of apoptosis. This was associated with G2/M phase cell cycle arrest, down regulation of anti-apoptotic (Bcl-2, Bcl-xL, survivin, IAP-1, and IAP-2) and proliferative (cyclin D1) proteins, activation of caspase-3, and PARP cleavage [31].

Lantana camara L.

Lantana camara L. is a species of the *Verbenaceae* family which

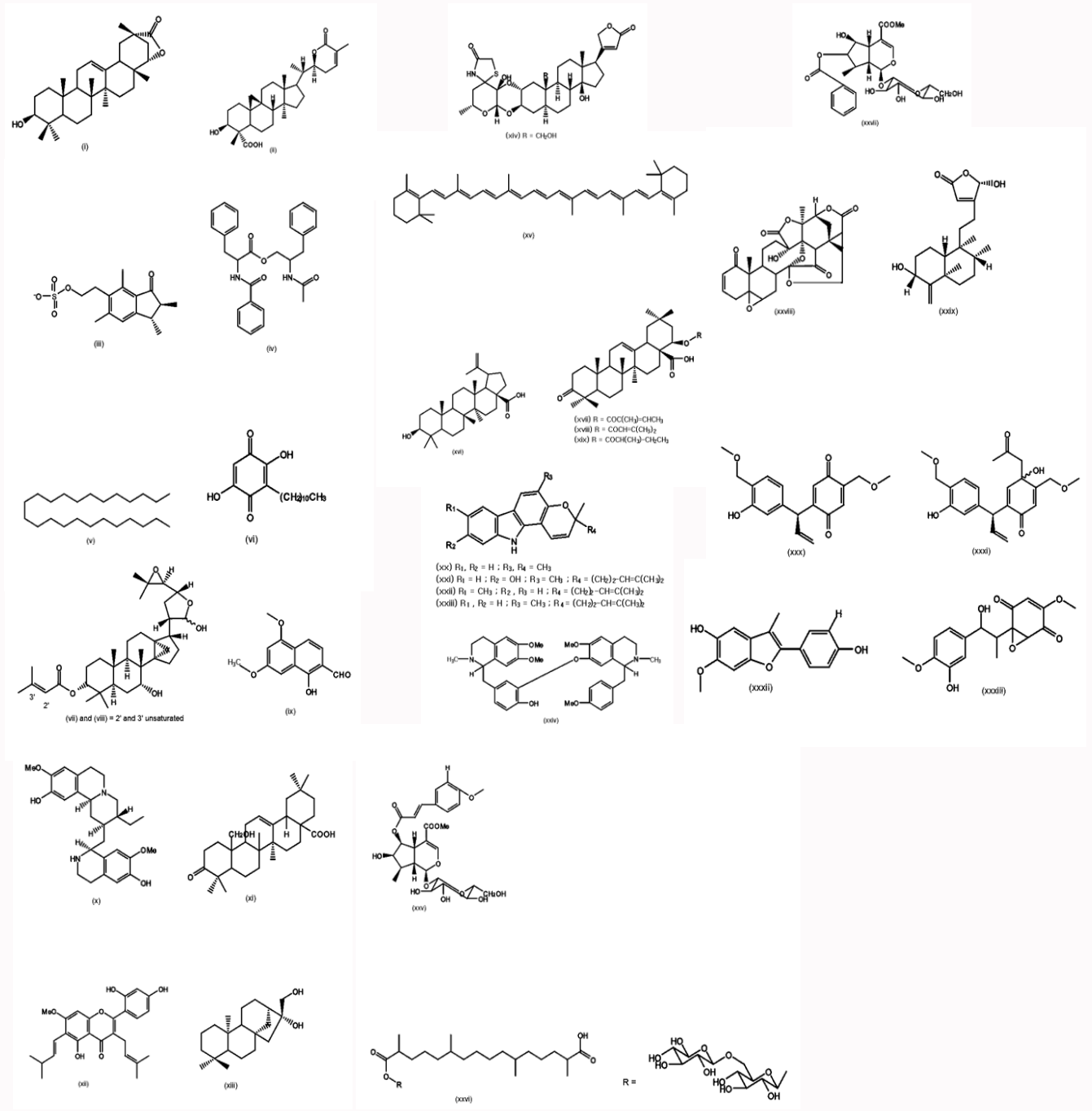

Figure 1: Chemical structures of SAARC-originating compounds showing activity against breast cancer.

is commonly known as "Spanish Flag." The extract obtained from *L. camara* exhibits anticancer activity by inducing apoptosis in MCF-7 cells. Mechanistic studies have revealed a regulatory effect of *L. camara* on the Bcl-2 family proteins including Bid, Bax, Bcl-2, caspase-8, caspase-9, and PARP [51]. Furthermore, Lantadenes A (xvii), B (xviii), and C (xix) and 22β-dimethylacryloyloxy-24-hydroxy-3-oxo-olean-12-en-28-oic acid were isolated from the leaves of *L. camara*. They exhibited weak to moderate cytotoxic activity in MCF-7 cells through the Bcl-2 gene family and also through their binding to the antiapoptotic Bcl-xL protein, which is capable of disrupting the Bcl-xL/Bak association [52,53].

Murraya koenigii Linn.

Murraya koenigii Linn., belongs to the *Rutaceae* family and is commonly known as the "Curry leaf tree." It is known locally as "Bar Sunga" in Bangladesh, "Mitha neem" in India, and "Karapincha" in Sri Lanka. Non-polar extracts of *M. koenigii* cause a potent cytotoxic effect in various cancers [54]. Ghasemzadeh et al. [55] showed that the leaf extract of *M. koenigii* exhibits significant anticarcinogenic effects in MDA-MB-231 cells, resulting from the presence of various flavonoids, such as quercetin, catehin, epicatechin, naringin, and myricetin. Moreover, various carbazole alkaloids, namely girinimbine (xx) mahanine (xxi), mahanimbicine (xxii), and mahanimbine (xxiii) were isolated from *M. koenigii* and exhibited significant antitumor

activity in MCF-7 cells [56,57].

Nelumbo nucifera Willd.

Nelumbo nucifera Willd., belongs to the Nelumbonaceae family and is popularly known as "Sacred Lotus". The hydroalcoholic extract of *N. nucifera* leaves exhibits anticancer effects in MCF-7 cells by causing G0/G1 phase cell cycle, inducing p53 phosphorylation and p21 expression, and downregulating the expression of cyclins and cdk molecules, possibly by the effects of gallic acid, rutin, and quercetin [58,59]. Moreover, neferine (xxiv), a major bisbenzylisoquinoline alkaloid isolated from the embryos of *N. nucifera*, exhibited significantly enhanced ADM cytotoxicity in the multidrug resistant MCF-7/ADM cells and promoted ADR-mediated apoptosis in MCF-7/ADM cells in a dose-dependent manner [60].

Nyctanthes arbor-tristis L.

Nyctanthes arbour-tristis L., commonly known as "Night Jesmine," is a member of the *Oleaceae* family and is locally known as "Sheuli" in Bangladesh, "Harsingar" in India, and "Sepalika" in Sri Lanka. The methanolic extract of the dried leaf, fruit, and stem exhibited cytotoxicity against MDA-MB-231 cells [61]. To date, iridoid glycoside Arbortristoside A (xxv) and its synthetic derivatives have shown anticancer activity against MCF-7 and MDA-MB-231 cells through cell cycle arrest and caspase-3-dependent apoptosis [62]. Khanapur et al. [63] reported that the ethanol extract and ethylacetate fractions of *N. arbour-tristis* show potent cytotoxic activity against various breast cancer cells resulting from the presence of flavonoids, phenolics, Crocin-3 (xxvi), and Arborside C (*xxvii*).

Physalis minima L.

Physalis minima L. (*Solanaceae*) is commonly known as the "Sun Berry." The chloroform extract of *P. minima* caused significant growth inhibition of human T47D cells through p53, caspase-3, and c-myc-dependent apoptotic pathways [64]. Moreover, a panel of withanolides was identified from this plant and included physalin F (xxviii), which may act as a chemopreventative agent by triggering apoptosis by activating the caspase-3 and c-myc pathways in T47D cells [65,66].

Polyalthia longifolia Benth. & Hook. f.

Polyalthia longifolia cv. pendula (*Annonaceae*) is native to the drier regions of India and is known as "Ashoka." The chloroform fraction of *P. longifolia* induced apoptosis by increasing sub-G0 DNA fractions, a loss of mitochondrial membrane potential, cytochrome c release, activation of caspase-3 and -9, and PARP cleavage [67]. Clerodane diterpene and (-)-3 α,16 α -dihydroxycleroda-4(18),13(14) Z-dien-15,16-olide (xxix) were identified from the leaves of *P. longifolia* and exhibited strong apoptotic activity in MCF-7 cells [68].

Pterocarpus santalinus L. f.

Pterocarpus santalinus L. f., commonly known as "Red sandalwood," belongs to the Fabaceae family. Phytochemical studies have revealed the presence of neoflavonoids, S-3'-hydroxy-4,4'-dimethoxydalbergione (xxx), and pterolinus Hb (xxxi) in *P. santalinus*, and exhibited cytotoxicity in MDA-MB-231 cell lines. Benzofurans, pterolinus-B (xxxii), and pterolinus-D (xxxiii) was cytotoxic to MCF7 cells [69].

Solanum nigrum Linn.

Solanum nigrum Linn. (*Solanaceae*) is commonly known as "Black Nightshade." Crude extracts from *S. nigrum* induced a significant cytotoxic effect against MCF-7 cells by inducing apoptosis and/or autophagocytosis [70]. At high concentrations, crude extract of *S. nigrum* inhibited p-Akt levels and caused cell death resulting from the induction of autophagy and apoptosis in AU565 cells by flavonoids, including gentisic acid, luteolin, apigenin, kaempferol, and m-coumaric acid [71]. A 150-kDa phytoglycoprotein isolated from the plant showed inhibitory effects on the DNA-binding activities of TPA-induced NF-κB and AP-1 as well as an enhancing effect on NO production, which plays an important role in MCF-7 cell cytotoxicity [72,73].

Future Perspectives and Conclusion

The identification of plant-derived lead compounds as potential chemotherapeutic agents has enhanced research focused on botanical diversity. Exploration of plant and plant-derived compounds from unexplored areas is expected to provide several new or analogous molecules that exhibit significant therapeutic activity and less toxicity compared with currently available chemotherapeutic drugs. Not only do new, effective therapies with novel mechanisms of action improve our understanding of disease, but they lead to the development of future anticancer drugs. The development of new molecular biological techniques has also facilitated the identification of individual components in key cell systems, increased our understanding of cancer therapy, and provided a basis for elucidating the underlying mechanisms of many drugs. Furthermore, they have enabled scientists to produce individual proteins or related human homologs for structural study and for use in the screening of natural compounds. Similarly, developments in instrumentation, such as high-throughput screening, has facilitated the analysis of a large number of compounds for anticancer activity.

The geographic and environmental variation among the SAARC countries provides rich plant diversity. However, because of a lack of advanced research facilities and funds, the development of natural anticancer agents has been hindered. The present review focused on research trends using breast cancer cell lines, such as MCF-7, MDA-MB-231, MDA-MB-235, MDA-MB-435S, T47D, and AU565. We also summarized the results of natural products in sensitive and resistant breast cancer cells since overcoming drug resistance is a major limitation to the successful treatment of breast cancer. This brief review examined unique plant-derived molecules from SAARC and their mechanisms of action against breast cancer. As the interface between chemistry and biology narrows and the demand for cost-effective medication and biological agents from sustainable resources increases, the study of plant extracts and their active compounds for anticancer properties will only increase.

Synergistic effects can maximize the therapeutic efficacy of anticancer drugs [74]. In a recent study, we demonstrated the optimum effect of three polyphenol compounds by establishing combination indices [75]. This strategy may be applied to breast cancer studies by (1) identify synergistic effects between compounds in the plant itself, (2) comparing the synergistic effects between plant-derived natural products and compounds or existing anticancer drugs, and (3) comparing natural products derived from plants with marine or other natural products. Natural anti-breast cancer substances with excellent efficacy may be evaluated for synergistic activity through various approaches such as in silico prediction, docking simulation, quantitative structure-activity relationship, and prediction of activity spectra for substances. When active compounds from natural products or foods exert a synergistic effect on a molecular target in breast cancer, we expect to observe robust anticancer effects.

Acknowledgment

Md Badrul Alam and Hee-Jeong Choi are supported by BK21Plus Creative Innovative Group for Leading Future Functional Food Industry, Kyungpook National University.

Funding

This study was supported by the National Research Foundation of Korea (NRF) grant, funded by the Ministry of Science and ICT (2020R1A2C2011495).

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