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Review Article

ANTI–BREAST CANCER FROM VARIOUS NATURAL SOURCES, REVIEW

M. ABD ELGADIR[1], MOHAMED SALAMA[2], AISHAH ADAM[3]*

[1,3]Pharmacology and Toxicology Laboratory, Faculty of Pharmacy, Universiti Teknologi Mara, 42300 Bandar Puncak Alam, Selangor, Malaysia, [2]Department of Pharmaceutics, Faculty of Pharmacy, Universiti Teknologi Mara, 42300 Bandar Puncak Alam, Selangor, Malaysia.
Email: mam.uitm2011@gmail.com

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ABSTARCT

The objective of this paper was to highlight some natural anti-cancer particularly used for breast cancer. In this paper, some evidence for the success of using natural products as anti-cancer, selected *in vitro* and *in vivo* studies on anti-cancer plants were summarized from many studies which recently conducted with the objectives of using natural sources against breast cancer. It was found that theanti-cancer activities of the plants used in this regard were highly dependent on their components of major types of phenolic compounds present in the plants. The information provided in this paper could assist in building strong ideas about the ability of natural sources of anti-breast cancer as well as conducting deep researches in such fields of studies.

Keywords: Breast cancer, Natural sources, Phenolic compounds, Tumor.

INTRODUCTION

Breast cancer is considered as the second most common cancer-related cause of death among females. It caused a major public health concern and accounting for nearly 1 in 3 cancers diagnosed among women [1]. It is one of the main life-threatening diseases that a woman may have to face during her lifetime [2]. An increasing incidence of breast cancer reported over the last few decades has led to development of new anti-cancer drugs particularly from natural sources [3,4] which showed large amount of scientific evidence in lowering the risk of cancer [5-7]. Experimental investigations demonstrated that many naturally occurring agents and plant extracts have shown anti-cancer potential in a variety of bioassay systems and animal models [8, 9]. These anti-cancer activities of the extracts from medical plants were associated with their components of phenolic compounds; the major types of phenolic compounds which include flavonoids, phenolic acids, coumarins, tannins, lignans, quinones, curcuminoids and stilbenes [10, 11]. Recently, there are many studies conducted with the objective of using plants as anti-cancer natural sources against breast cancer [12-18]. This paper summarizes selected studies investigated to reduce the risk of breast cancer using natural products.

Some evidence for the success of using natural products as anti-cancer

Historically, plants and their derived products have been used for long time in the treatment of cancer. For instance, more than 3000 plant species are listed and used as anti-cancer ones [19]. In traditional medicine systems, plants are recognized and played an important dominant role in the development of such systems. As reported by WHO, approximately 80% of the population in some African and Asian countries depend on traditional medicine for primary health care [20]. It was reported that by 2050, the global market for herbal products is expected to reach $5[21]. Plant based drug discovery not only resulted in development of many anti-cancer drugs but also provides a platform for design of safe and novel drugs. These could be in terms of proper understanding of many interactions between complexes synergistic of various constituents of anti-cancer herbs [22]. Verma and Singh [23] isolated two alkaloids namely vinblastine (1) and vincristine (2) from the Madagascar periwinkle. They can be used in clinical oncology for blocking the polymerization of tubulin molecules into micro-tubules as well as preventing the formation of the mitotic spindle which result in metaphase arrest and apoptosis [24]. One good example of anti-cancer plants is curcumin which is the principal curcuminoid and responsible for the yellow colour of the spices. It comprises approximately 2–5% of turmeric as well as the majority of turmeric's therapeutic effects [25]. Curcumin also poses varieties of therapeutic properties such as anti-inflammatory, antiseptic, anti-oxidant and analgesic activities. It was found that curcumin had effects on many biological pathways as well as anti-cancer activities involved in oncogene expression, mutagenesis, tumorigenesis, apoptosis, cell cycle regulation and metastasis [25]. However, further evidence for the success of natural product drug discovery, the discovery of paclitaxel (Taxol, 9) which extracted from the bark of the Pacific Yew, Taxusb revifolia Nutt (Taxaceae). It considered as the first compound discovered to promote microtubule formation and has been used in the treatment of several types of cancers such as breast cancers ovarian ones [35]. Numerous of paclitaxel semisynthetic derivatives has been developed later and the first effective one to reach clinical use was docetaxel (10) which have shown significant clinical activity in a different toxicity pattern and a wide range of tumours [36,37]. However, several other derivatives from paclitaxel such as paclitaxel microspheres and albumin-bound docetaxel are still in clinical development [38].

Selected *in vitro* studies on anti-cancer plants

An *in vitro* study refers to the technique of performing a given procedure in a controlled environment outside of a living organism. Wang et al. [39] investigated anti-cancer activity of litchi fruit pericarp (LFP) extract which contains significant amounts of polyphenolic compounds. Human breast cancer cells were tested *in vitro* for cytotoxicity, colony formation inhibition, BrdU incorporation and gene expression profiling after treatment with LFP extract. It exhibited powerful antioxidative activity against fat oxidation *in vitro*. LFP extract demonstrated a dose-and time-dependent inhibitory effect on cell growth (IC50 = 80 µg/ml).

It was suggested that LFP extract might have potential anti-cancer activity on different types of breast cancers. This finding could be attributed to many factors such as DNA damage effect of the extract, its down-regulation of multiple genes involved in cell cycle regulation, proliferating inhibition and apoptosis induction of cancer cells through up-regulation and cell proliferation, signal transduction and transcriptional regulation, motility and invasiveness of cancer cells, apoptosis and Hyaluronan-mediated motility receptor (HMMR). An anti-cancer activity of Cajanol which is chemically recognized as (5-hydroxy-3-(4-hydroxy-2-methoxyphenyl)-7-methoxychroman-4-one) is an isoflavanone from Pigeonpea [Cajanuscajan (L.) Millsp.] roots were investigated on cancer cells [12].

Table 1: Selected plant compounds with anti-cancer properties

S. No.	Family of the plant	Plant species	Plant part	Extract solvent	TGI (µg/ml)
1	Anacardiaceae	*Rhusleptodictya*Diels.	Leaves	DCM	55.42
2	Apocynaceae	*Gomphocarpusphysocarpus* Schltr	Roots	DCM: MeOH	20.80
3	Apocynaceae	*Gomphocarpusfruticosus* Dryand.	Leaves and stems	MeOH	4.78
4	Asparagaceae	*Asparagus aethiopicus*L	Roots	DCM: MeOH	15.00
5	Asteraceae	*Brachylaenarotundata*S. Moore	Leaves	DCM	25.95
6	Bignoniaceae	*Kigeliaafricana*(Lam.) Benth.	Leaves	DCM	15.00
7	elastraceae	*Gymnosporiatenuispina*(Sond.)Szyszyl.	Stems	MeOH	28.04
8	Fabaceae	*Erythrinalysistemon* Hutch.	Whole plants	DCM: MeOH	15.00
9	Geraniaceae	*Pelargonium acraeum*R. A. Dyer	Whole plants	H2O	12.74
10	Iridaceae	*Moraeapolystachya*(Thunb.)	Whole plants	DCM: MeOH	29.63
11	Capparaceae	*Cadabaaphylla*(Thunb.) Wild	Roots	DCM	14.89
12	Convolvulaceae	*Ipomoea cairica*(L.) Sweet	Whole plants	DCM: MeOH	65.34
13	Crassulaceae	*Kalanchoethyrsiflora*Harv.	Leaves and roots	MeOH	15.00
14	Solanaceae	*Physalisperuviana*L.	Leaves	DCM: MeOH	35.59
15	Solanaceae	*Solanumtomentosum*L.	Stems	H2O	14.68
16	Celastraceae	*Gymnosporiatenuispina*(Sond.)	Flowers and leaves	MeOH	28.04

DCM = dichloromethane, MeOH = methanol, TGI = total growth inhibition, *Reference: [34].

Table 2: Selected plants inhibiting breast MCF7*

S. No.	Plant source	Anti-cancer compound	Effect as anti-cancer	References
1	*Sanguinariacanadensis, Argemonemexicana, Papaver somniferum*(Opium poppy	Sanguinarine	Decreases histone methylation (H3K4 and H3R17); HMTi (G9a), *in vitro* HATi and decreases histone acetylation	[26]
2	*Puerariamirifica, Pueraria lobata, Glycine max* (soy)	Daidzein	Gene reactivation (p16, RARbeta, and MGMT), induces DNA demethylation	[27]
3	Silybummarianum (milk thistle)	Silibinin	Increases histone acetylation	[28]
4	*Curcuma longa* (curcuma)	Curcumin	Decreases histone and protein acetylation, increases histone acetylation, reduces expression of several HDACs sequence-specific demethylation at promoter regions of epigenetically silenced genes	[29,30]
5	Fruits and vegetables	Quercetin	Induces gene expression and demethylation promoter	[31]
6	*Rosmarinusofficinalis* (Rosemary)	Rosmarinic acid	*Decreases* DNMTi *in vitro*	[32]
7	*Caesalpiniasappan*	Brazilin	HDAC2 expression, increases histone acetylation and Downregulation of HDAC1	[32]
8	Some fruits such as mango, blackberry and a number of plants such as tea, areca nuts	Gallic acid	Decreases protein acetylation (NF-κB p65) and *in vitro* HATi (p300, CBP, PCAF, Tip60)	[33]
9	Olives, green tea	Protocatechuic acid	*In vitro decreases* DNMTi	[32]
10	*Allium* sp. (onion, garlic, shallots)	Diallyl disulfide	increases histone acetylation	[33]

It inhibited the growth of MCF-7 cells. The results also showed that the IC50 value was 54.05µM after 72 h of the treatment, 58.32 µM after 48 h and 83.42 µM after 24 h. Cajanol arrested the cell cycle in the G2/M phase and induced apoptosis via a ROS-mediated mitochondria-dependent pathway and initiated apoptosis. To the best of our knowledge, this is the first report demonstrating the cytotoxic activity of cajanol towards cancer cells *in vitro*. Human breast cancer (MCF-7) cells were treated with GI50 concentration (concentration of lectin required for 50% inhibition of cell growth) extracted from mulberry leaf lectin (MLL) at dose of 8.5 lg/ml for a period of 24 h to induce cell death [15]. It was found that MLL induced cell death through apoptosis in MCF-7 cells. Chalcones, the biosynthetic precursors of flavonoids present in edible plants was examined for its effect on breast cancer using TNBC cells [45]. The treatment was conducted with chalcone derivatives, 2-hydroxychalcone, and xantho humol for 24 h. The results revealed great inhibition of the growth of MDA-MB-231cells with IC50 values of 18.1, 4.6, and 6.7 lM, respectively. These results suggest a potential application of these chalcones as anti-cancer agents which can alleviate malignant progression of TNBC. Sahpazidoua et al. [18] examined extracts of grape for their ability to inhibit growth of breast cancer (MCF-7 and MDA-MB-23). The cancer cells were exposed to the extracts for 72 h and the effects on cell growth were evaluated. The results showed that the grape extracts inhibited cell proliferation with IC50 values of 121–230 µg/ml for MCF-7 and 121–184 µg/ml for MDA-MD-23.

Selected *in vivo* studies on anti-cancer plants

An *in vivo* study (Latin for "within the living") refers to experimentation using a whole, living organism as opposed to a partial or dead organism. Animal studies and clinical trials are two forms of *in vivo* research. Anti-cancer activity of litchi fruit pericarp (LFP) extract on human breast cancer was confirmed with *in vivo* study using nude mice bearing human breast infiltrating duct carcinoma orthotopically by oral administration of 0.3% (0.3 mg/ml) of LFP water soluble crude ethanolic extract for a period of 10 weeks [39]. The result revealed that 40.7% reduction in tumor mass volume and significant increases in casepase-3 protein

expression (casepase-3 protein involved in various biological functions such as apoptosis, cell proliferation, cell cycle regulation, signal transduction and transcriptional regulation, extracellular matrix/adhesion molecules and malignancy of cancer cells) were observed in the experiment. Wu et al. [40] studied whether psoralen which known as a coumarin isolated from the seeds of P. corylifolia L. and it has been reported [41] to have an antioxidant activity can inhibit metastasis of breast cancer to bone *in vivo* in mice. The molecular, histological biological and imaging studies showed that the psoralen inhibits bone metastases and led to inhibition of breast cancer cell growth in the bone microenvironment which suggested that psoralen is a bone-modifying agent and a potential therapeutic to treat patients with bone metastases. In another research, Noratto et al. [42] examined tumor growth inhibition and anti-metastatic effects of peach polyphenolics *in vivo* using a xenograft model and MDA-MB-435 breast cancer cells. The results revealed that tumor growth and lung metastasis were inhibited *in vivo* by peach poly phenolics in a dose range of 0.8 – 1.6 mg/day. Gene expression studies were also conducted to confirm these effects using mediated by inhibition of metalloproteinases. Modulation of metalloproteinase-2 (MMP-2), metalloproteinase-3 (MMP-3) and metalloproteinase-13 (MMP-13) gene expression may be some the molecular targets for anti-metastatic activity of peach polyphenolics. These compounds may constitute a novel chemopreventive tool to reduce the risk of metastasis in the combination therapy when primary cancer is diagnosed. The studies suggested a conversion to equivalent human intake for future clinical studies using the body surface area (BSA) normalization method at a dose of ~370.6 mg/day for a human adult of 60 kg, which can be supplied by consuming 2 to 3 peach fruit per day or alternatively using a dietary supplement peach polyphenol extract powder.

CONFLICT OF INTERESTS

Declared None

CONCLUSION

This review article reports selected investigations using natural plants as breast cancer medication. The anti-cancer activity of these plants was associated with their components of major types of phenolic compounds such as phenolic acids, flavonoids, tannins, lignans, quinones, coumarins, curcuminoids and stilbenes.

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