MALAYSIAN MEDICINAL PLANTS' POTENTIAL FOR BREAST CANCER THERAPY

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ABSTRACT

Objective: This review focused on Malaysian medicinal plants that have been evaluated and pose potentials to treat breast cancer.

Methods: Google Scholar, Web of Science, PubMed, Scopus, Biomed, ResearchGate, academia.edu, IEEE Xplore, ScienceDirect, and Ingenta databases were searched for this review and studies reported between January 1st, 2010 and June 30th, 2016.

Results: A total of 105 plants species representing 54 different families and 79 genera were reviewed. 97% of the plants were tested using MCF-7 and MDA-231 breast cancer cell lines and exhibited most significant *in vitro* anticancer activity, and 3% were tested using another type of breast cancer cell lines. Most of the bioactive compounds of the medicinal plants that exhibited good activity (IC_{50} values <120 µg/mL) are a group of phenols, alkaloids, flavonoids, terpenoids, and saponins. Induction of apoptosis was found to be the significant cell death pathway.

Conclusion: This article reviews the available literature concerning research on anti-breast cancer plants. Furthermore, identification and characterization of active components and toxicology evaluation also need to be studied in details and also point out their clinical trials.

Keywords: Breast cancer, Medicinal plants, Bioactive components, Anticancer mechanism.

INTRODUCTION

Cancer

Cancer is a group of diseases characterized by abnormal cell growth with the potential to affect to other parts of the body. Cancer is a condition that is related to an enormous cluster of diseases that disturb every region of the physique [1]. The World Health Organization (WHO) categorized cancer among the non-contagious disease which accounts for 63% of deaths globally [2]. Cancer is an intricate disease condition affecting millions of people all over the world [3].

Cancer epidemiology

Cancer is one of the principal reasons for fatality rate in the world, with roughly 14 million different events and also 8.2 million cancer-linked deaths in 2012 [4,5]. Death of individuals with cancer is increasing rapidly. The WHO reported that cancer accounted for 13% of world death that is about 7.6 million in 2005, and this percentage is expected to increase every year [6]. The number of new cases is likely to increase by 70% in the next two decades [2,7].

Breast cancer

Breast cancer is the most common cancer of women in Malaysia, with a prevalence of 86.2 per 100,000 women in 1996 [8]. Breast cancer comprised 30.4% of all female cancers in Malaysia, and this was higher compared to previous reports in Sabah with 18%, Kuala Lumpur (10.7–13.8%), and Singapore with 13% [9].

The WHO figured that, without abrupt action, the number of mortality caused by cancer would rise approximately 80% by 2030 with most occurring in low- and middle-income countries [10]. Siegel *et al.* [7] reported that 21.7 million cancer cases are expected to be diagnosed in 2030. In Malaysia, the second most communal source of death is cancer after heart-related diseases, and the dominant cancers are lung, breast, cervix, and leukemia [11]. It was estimated that yearly rate of cancer in Malaysia is 30,000. In 1998, the population of Malaysia was 21.4 million, and the number of cancer is projected to grow in aged population by 2020 [12].

Cancer chemotherapy

Cancer chemotherapy represents an option for patients with breast cancer when an indication for chemotherapy is given to weaken and destroy cancer cells in the body, including cells at the original cancer site and any cancer cells that may have spread to another part of the body [13]. Breast chemoprevention can be defined as "the use of pharmacologic or natural agents that inhibit the development of invasive breast cancer either by blocking the DNA damage that initiates carcinogenesis or by arresting or reversing the progression of pre-malignant cells in which such damage has already occurred [14]. Unfortunately, this treatment has not been fortunate enough to impart significant improvement in the morbidity or mortality of breast cancer due to the severe side effects; this cancer is highly resistant to chemotherapy as no effective treatment exists for advanced disease conditions [15]. The most common drugs used in the treatment of breast cancer chemotherapy are tamoxifen [16], raloxifene [17], aromatase inhibitors [18], polymerase inhibitors [19], and trastuzumab [20]. Other drugs include anthracyclines, taxol, cyclophosphamide, carboplatin, docetaxel, paclitaxel, cisplatin, carboplatin, vinorelbine, capecitabine, doxil, gemcitabine, mitoxantrone, and ixabepilone.

Cancer cell resistance to chemotherapy is still a heavy burden that impairs treatment of cancer patients. Both intrinsic and acquired resistance results from the numerous genetic and epigenetic occur in cancer cells. Most of the hallmarks of cancer cells provide general mechanisms to sustain stresses such as the ones induced by chemotherapeutic drugs. Moreover, specific changes in the target bring resistance to specific drugs such as modification in nucleotide synthesis enzymes on antimetabolite exposure, in microtubule composition on spindle poison treatment, in topoisomerase activity on topoisomerase inhibitor incubation, or intracellular signaling pathways when targeting tyrosine kinase receptors [21]. The first

cause of therapeutic failure results from genetic alterations existing before treatment; this is the primary or intrinsic resistance. The second one is induced by drug treatment and is called secondary or acquired resistance. Both are due to mutations in the genome of cancer cells and to epigenetic changes. Unfortunately, resistance appears not only to conventional chemotherapy but also to targeted therapies, the so-called smart drugs to standard chemotherapy such as kinase inhibitors and tamoxifen that binds to the estrogen receptor (ER) [21,22]. However, due to the shortcomings of modern treatment, nowadays, finding active complexes of the plant has been accelerated using modern techniques, and this has resulted in plants recycle. Thus, drugs that are produced from herbal plants are usually specialized in treating chronic disease like cancer [23]. Many plants with cancer-fighting properties were identified which have a high attraction to a biological target and their strength to inhibit the cancer metastasis is studied widely. Active components from some medicinal plants are yet to be identified, but crude extracts display cytotoxic action against most of the human cancer cell lines. Knowledge of these indigenous anticancer plants forms the platform for new, safe, and effective drug development [24].

Although the use of plants for cancer remedy has been traced for the past four decades with many of articles, but so far in the past 10 years, there were only 2 major reviews and other few mini-reviews that reviewed the medicinal plants use in the treatment of breast cancer in another part of the world. In 2012, Nagaprashanthi *et al.* [25] reviewed 56 important ethnomedicinal plants (indigenous system of medicine) evidenced for breast cancer by the scientific study [25]. They published a full-length paper on ethnobotanical survey and digitization of medicinal and aromatic plant-based foods for effective breast cancer treatment, by randomly administering semi-structured questionnaires to 70 physicians and interviewed 500 complementary and alternative medicine practitioners, and 78 plants were reviewed [26]. Lakshmi [27] reviewed and compiled data of anticancer activity of three traditional herbs, namely, *Zingiber officinale*, *Semecarpus anacardium,* and *Fagonia cretica*. Another review by Islam et al., [28] published their review of herbal medicinal plant in the treatment of breast cancer and relationship between medicinal herbs, and some tumour suppressor molecules focused on gene expression and posttranslational modifications, and some tumor suppressor molecules focused on gene expression and post-translational modifications [28]. Dembitsky [29] published a review paper on anti-breast cancer agents derived from plants analyzing anti-breast cancer potencies of quite a few extracts from different plant sources and compared their anti-proliferative efficiency of crude extracts with actions of their purified ingredients [29]. A review by Elgadir *et al.* [30] highlighted ten anticancer plants particularly used for breast cancer and outlined some evidence for the success of using natural products as anticancer with selected *in vitro* and *in vivo* studies on anticancer plants with their anticancer compounds and their effects as anticancer. Jaikumar and Jasmine [31] considered 58 medicinal plants from various families that have inhibited cell growth at different IC_{50} values against MCF-7 [31]. Another editorial titled "natural cures for breast cancer treatment," focused on the biochemical properties of different types of plants that retain the immune stimulating and anti-tumour properties [32]. However, of the reviews above, only one review is from Malaysia and only ten medicinal plants were reviewed, that is, what motivate the writers to look back due to huge individual articles on breast cancer medicinal plants but yet review articles are lacking.

The general mechanism of cancer therapy
The general mechanism of cancer therapy includes antiproliferation of cells directly by enhancing killer cell activity naturally and promoting macrophage phagocytosis, stimulating apoptotic cancer cells through rising the output of immunoglobulin, nterleukin2, blood serum complement and interferon, necrosis enforcement of the tumor, preventing translocation of tumor, and disseminate by obstruction the tumor tissue source of blood, improving the quantity of platelets and leukocytes through motivating the hemopoietic role, encouraging the opposite transformation from tumor cells into regular cells, helping metabolism and averting carcinogenesis of regular cells and lastly

appetite stimulation, relieving pain, improvement in sleeping quality, and hence benefiting patients' well-being [33]. While the mechanism of breast cancer therapy is likely to be in connection with molecular mechanisms of antiestrogen therapy and endocrine resistance to treatment all stages of breast cancer. Recent studies shows that tamoxifen and the new pure antiestrogens appear to have different mechanisms of action: Tamoxifen and related compounds cause a change in the folding of the steroid binding domain that prevents gene activation, whereas the pure antiestrogens cause a reduced interaction at response elements (RE) and cause a rapid loss of receptor complexes. Tamoxifen treatment produces the changes in the cellular and circulating levels of growth factors that could influence both receptor-negative or receptor-positive tumor growth and the metastatic potential of a tumor [34,35].

Mechanisms of ER action in breast cancer
Genomic activity of estrogen bound ER, crosstalk with growth factor receptor tyrosine kinases such as EGFR, HER2, and IGF1- R) and with additional signaling and coactivator molecules activates multiple downstream kinase pathways (e.g. PI3K/AKT-mTOR and Ras/p42/44 MAPK) which in turn phosphorylate various transcription factors (TFs) and coregulators, including components of the ER pathway that enhances gene expression on EREs and other RE. The non-nuclear/non-genomic activity, which can also be activated by tamoxifen, is enhanced in the presence of overexpression and hyperactivation of RTKs and can contribute to endocrine therapy resistance. Overall, the nuclear/genomic and non-nuclear/non-genomic ER activities work in concert to provide breast tumor cells with proliferation, survival, and invasion stimuli. Signaling from the microenvironment activates stress-related pathways, and members of the integrin family interact with downstream kinase pathways that can further modulate of the transcriptional machinery including ER [36].

METHODS
Google Scholar, Web of Science, PubMed, Scopus, BioMed, ResearchGate, academia.edu, IEEE Xplore, ScienceDirect, and Ingenta databases were used for this review and paper selected between January 2010 and June 2016 (5 years). The search terms used are "cancer" and "breast cancer," "anticancer plants," "Medicinal Plants," "traditional medicine," "anti-breast cancer plants," or "herbs" without narrowing or limiting search. Reports with available abstracts, methods, discussion, and conclusion were reviewed.

RESULTS AND DISCUSSION

Malaysia is rich in biodiversity and has hundreds of flora that are used in traditional medicine and many more used in general folklore medicine. The plants were shown to produce additional information such as their phytochemical constituents (bioactive compounds), pharmacological properties, and their mechanism of action. Majority of the plants screened for anticancer properties have been used in either traditional medicine or as food. The use of traditional medicine has expanded, and health supplement consisting of different types of herbal medicines has become very popular in Malaysia in the recent years. The widely consumed plants as food additive and medicine are believed to possess anticancer potentials [37].

Medicinal plants have played an important role in the treatment of breast cancer. In this review, 100 anti-breast cancer plants belonging to 54 families and 79 genera have been presented in scientific, common local, and family names. Part and solvent used, active component(s) identified, breast cancer cell line and mechanism of action were also presented (Table 1). From Table 1, 22 species representing 22% of the total plants demonstrates strong anticancer activities such as *Annona squamosa* with IC_{50} value of 10 μg/mL, *Bauhinia purpurea* with IC_{50} value of 9 μg/mL for MCF-7 and IC_{50} value of 17 μg/mL for MDA-231, *Calotropis gigantea* with IC_{50} value of 1.3 μg/mL for MCF-7 and IC_{50} value of 3.3 μg/mL for MDA-231, *Piper nigrum* with IC_{50} value of 13 μg/mL, *Casearia capitellata* with IC_{50} value of 2 μg/mL in MCF-7, *Hedyotis*

Table: 1 List of medicinal plants traditionally used in the management of breast cancer

Plant name/common name	Family	Local name (Malay)	Active compound	Experimental model	Mechanism of action	Source
Abrus precatorius/jequirity	Fabaceae	Saga	Lectin	MDA-MB-231. (*in vitro*)	Significant morphological changes such as shrinking of cytoplasm, condensation of nucleus, and formation of membrane-bound vesicles	[39,59,84]
Albizia zygia/Albizia	Leguminosae	Pukul lima	Budmunchiamines A, B, and C	MCF-7 (*in vitro*)	Cytotoxic to MCF-7 at IC_{50} values of 83.16 μg/mL and 57.54 μg/mL	[112,113]
Allium cepa (Onion)	Liliaceae		Diallyl trisulfide	MCF-7 (*in vitro*)	Increase histone acetylation	[30]
Allium sativum/garlic	Liliaceae	Bawang putih	Allicin, alliin, diallyl trisulfide	MCF-7 (*in vitro*)	Stimulating the lymphocytes and macrophages is that they kill the cancerous cells and interferes with tumor cells metabolism	[30,32,33,60]
Alpinia conchigera	Zingiberaceae	Lengkuas ranting	1'-(S)-1'-Acetoxychavicol acetate (ACA)	MCF-7 (*in vitro*)	ACA induced cell cycle arrest at the G0/G1 phase at IC_{50} values 34.0 μM to 48.0 μM	[110]
Alpinia officinarum/lesser galangal	Zingiberaceae		Flavonol galangin	MCF-7. (*in vitro*)	Induced an increase in the proportion of cells in the S-phase in a dose-dependent manner. Particularly, the cell population in the S-phase was 12.90% in the untreated control group. After 48 h of incubation with 100 μg/mL extract, the S-phase population was significantly enhanced to 25.69%	[108,114]
Alternanthera tenella	Amaranthaceae		AgNPs	MCF-7. (*In vitro*)	AgNPs inhibited cell migration after 24h of treatment. The IC_{50} value of 42.51 g/mL. The AgNPs showed a significant reduction in the migration of MCF-7 cells	[115]
Alstonia scholaris /blackboard/scholar tree	Apocynaceae	Pulalinlin	Alstonine, ditamine, echitenine, and villalstonine	EAC (*in vitro*)	Reduce the tumor multiplicity incidence, decline in the glutathione levels and increased the lipid peroxidation	[54,55]
Amaranthus lividus/slender amaranth	Amaranthaceae	Bayamhijau	β-carotene and amygdalin	MCF7 and MDA-MB-231 (*in vitro*)	Inhibiting peroxidation of phosphatidylcholine liposomes persuaded with Fe3+/ ascorbate to scavenge ABTS, DPPH and hydroxyl radicals, to lessen Fe (III) to Fe (II) and to chelate Fe (II)	[58,87]
Amaranthus gangeticus/red spinach	Amaranthaceae	Ayam Merah	Carotenoids and ascorbic acid	MCF-7 (*in vitro*)	Antiproliferation of MCF-7 at IC_{50} values of 98.8 μg/mL	[51]
Andrographis paniculata/green chirayta	Acanthaceae	Hempedu Bumi	Andrographolide, diterpene lactone	MDA-MB-231 (*in vitro*)	Inducing apoptosis in the mutant p53, MDA-MB-231 anti-proliferative activity by mitochondria-dependent caspase-mediated pathway. Cell cycle arrest at G2 and M	[81,88,116]
Ardisia crispa/Christmas berry	Myrsinaceae	Mata Ayam	Benzoquinonoid, α, β-amyrin, and Ardisiacrispin A	MCF7 (*in vivo*)	AC7-1 said to inhibit B16- F10 melanoma cell adhesion to only specific synthetic peptides including RGDS inhibited both COX-1 and COX-2	[117,118]

(Contd...)

Table 1: (Continued)

Plant name/common name	Family	Local name (Malay)	Active compound	Experimental model	Mechanism of action	Source
Annona muricata/Soursop	Annonaceae	Durian belanda	Anonaine, isolaureline, annonamine	MCF-7 (*In vitro*) MCF-7, MCF-10A, MDA-231 and 4T1 cell line	Inhibit lipid peroxidation IC_{50} [MCF 7 = 220 μg/mL; MDA-MB231 = 3_{50} μg/mL; 4 T1 = 2_{50} μg/mL] MCF-10A was considerably higher than the three cancer cell lines (1000 μg/mL)	[49,57]
Annona squamosa/sugar apple	Annonaceae	Buahnona	Atisine, oxophoebine, and reticuline	MCF-7 (*in vitro*)	Anti-proliferation activity with IC_{50} value of 10ug/ml, of MCF-7 by apoptosis induction	[119,120]
Ardisia brevicaulis/coralberry or marlberry	Myrsinaceae	Mabberi	Ardisiacrispins A and B	MCF-7 (*in vitro*)	Inhibiting proliferation of via the activation of caspase-3 and caspase-9, up-regulation of the ratio of Bax/bcl-2 protein expression	[62]
Argemone mexicana/Mexican poppy	Papaveraceae		Sanguinarine and dihydrosanguinarine	MCF-7 (*in vitro*)	Decreases histone methylation (H3K4 and H3R17); HMTi (G9a), *in vitro* HATi and decreases histone acetylation	[30]
Artocarpus altilis/breadfruit	Moraceae	Sukun	Pyranocycloartobiloxanthone A, and B dihydro-artoindonesianin C,	MCF-7 (*in vitro*)	Exhibiting strong free radical scavenger towards DPPH with IC_{50} value of 2 μg/mL with prominent discoloration	[121,122]
Artocarpus obtusus/breadfruit	Moraceae	Lempoyang	Pyranocytoarlobito xanthone A	MCF7 (*in vitro*)	Caspase-3 and caspase-9 enzymes activation and upregulation of the ratio of Bax/bcl-2 protein expression	[50]
Azadirachta indica/neem tree	Meliaceae	Mambu	Azadirachtin, limonoid	MDA-MB 231 (*in vitro*)	Organelle organization alteration, cellular plan, and differentiation degree, cellular metabolism	[69]
Bauhinia purpurea/butterfly tree	Fabaceae	Tapakkuda	Bauhiniastatins, lutein, and B-sitosterolbauhinoxepin	MCF-7 and MDA-MB 231 (*in vitro*)	Active against MCF-7 at ($IC_{50} \approx 9$ μg/mL), and MDA-MB 231 at $IC_{50} \approx 17$ μg/mL)	[123,90]
Brassica oleracea/cabbage	Brassicaceae	Kubis	β-carotene, lutein, αTocopherol	MCF-7 (*in vitro*)	Apoptosis revealed that activated p53 caused up-regulation of Bax, Caspase-3 and downregulation of Bcl-2 proteins modulated signal transduction	[64,97,124]
Boswellia serrata/Indian olibanum	Burseraceae	Nhau	Boswellic acid	MCF-7 (*in vitro*)	Declined in polymorphonuclear leukocyte infiltration and migration, reduced primary antibody synthesis and nearly inhibited the classical complement pathway	[82,83]
Clausena excavata	Rutaceae	Daunsicerek, cherekhitam	Dentatin	MCF-7 (*in vitro*)	DTN treatment significantly arrested MCF-7 cells at the G0/G1 phase (p0.05), and ROS was significantly elevated. Moreover, DTN significantly blocked the induced translocation of NF-kB from the cytoplasm to the nucleus	[125]
Calotropis gigantea/crown flower	Apocynaceae	Remiga, kemengu	Calotropin, frugoside, calotoxin	MCF-7 and MDA-MB-231 (*in vitro*)	Inhibited MCF-7 and MDA MB-231 cells, IC_{50} of DCM extract with IC_{50} values ranging from 1.3 to 3.3 μg/mL	[126]
Capsicum annuum/red chilli	Solanaceae	Cili	Capsaicin, myricetin; a bioflavonoid	MCF-7 (*in vitro*)	Hindering production in LPS-stimulated RAW 264.7 macrophages	[127,128]

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Table 1: (Continued)

Plant name/common name	Family	Local name (Malay)	Active compound	Experimental model	Mechanism of action	Source
Carica papaya/pawpaw	Caricaceae	Betik	Ascorbic acid, carotenoids and glucosinolates	MCF-7 and MDA-MB-231	Induction of apoptosis on the proliferation of MCF-7 and MDA-MB-231 cancer cell lines after a 72 h treatment	[129]
Casearia capitellata	Flacourtiaceae	Similit Matangi	Genistein, glisitein, glycoside	MCF-7 (*In vitro*)	Exhibited by EA extract at IC_{50} value of 2 µg/mL on MCF-7	[65]
Catharanthus roseus	Apocynaceae	KemuntingCina.	Vinblastine and vincristine	Jurkat cell line (*in vitro*)	inhibiting the proliferation of the Jurkat cell line and promoting the growth of PBMCs	[66,98]
Centratherum anthelminticum/black cumin	Asteraceae	Kalajiri, somraj, cumin	Vernodalin	MCF-7 and MDA-MB-231 (*in vitro*)	Induced apoptosis marked by cell size shrinkage, deformed cytoskeletal structure and DNA fragmentation	[105]
Coriandrum sativum	Apiaceae	Ketumbar	αpinene, limppnene, γ-terpinene, p-cymene	MCF-7 (*in vitro*)	Antioxidant enzymes were disturbed leading to H_2O_2 rise; arrest made at the G2/M and apoptosis by the death receptor and mitochondrial pathways	[67]
Curcuma longa/Turmeric	Zingiberaceae	Kunyit	α-Turmerone, curcuminoids and curcumin curcumin	MCF-7 and MDA-MB-231 (*in vitro*) MCF-7 (*in vitro*)	Induced mitochondrial and nuclear DNA damage in cells and apoptosis Decreases histone and protein acetylation increases histone acetylation, reduces expression of several HDACs sequence-specific demethylation at promoter regions of epigenetically silenced genes	[30,33,37]
Coriandrum sativum/coriander	Apiaceae	Ketumbar	Flavonoids	MCF-7 (*in vitro*)	AgNPs inhibits the MCF-7 by the up-regulation of the p53 tumor suppressor gene expression and the subsequent rise in expressions of pro-apoptotic proteins like caspase-3,/ Bax and caspase-9	[95]
Cheilocostus speciosus/crêpe ginger	Costaceae	SetawarHutan	Costunolide	MCF-7 AND MDA-MB-231 (*in vitro*)	Overexpression of SOD and CAT inhibits tumor progression with less proliferation and migration of the cancer cells, reduction of oxidative stress-mediated DNA damage or mutations that induce carcinogenesis	[68,130]
Cymbopogon citratus/lemon grass	Poaceae	Seraimakan	N-methyl-N-nitrosourea	MCF-7 and MDA-MB 231, (*in vitro*)	DNA damage induced by MNU and a potential anticarcinogenic activity against mammary carcinogenesis in DDB-initiated female Balb/C mice	[131-133]
Curcuma amada/mango ginger	Zingiberaceae	Manjellakua	Curcuminoids	MDA-MB-231 and MCF-7 (*In vitro*)	Expression of hTERT mRNAs and not hTER were inhibited	[39]
Curcuma xanthorrhiza/false turmeric	Zingiberaceae	Temulawak	Xanthorrhizol, curcumin	MCF-7 (*in vitro*)	Inducing apoptosis through the modulation of Bcl-2, p53 and PARP-1 protein levels. effect on MCF-7 cells with an IC_{50} value of 1.71±0.16 µg/mL	[40]
Curcuma zedoaria	Zingiberaceae	Temuhitam	Alismol and curzerenone	MCF-7 (*in vitro*)	Anti-proliferation in MCF-7, HCT-116 and Ca Ski	[134]

(Contd...)

Table 1: (Continued)

Plant name/common name	Family	Local name (Malay)	Active compound	Experimental model	Mechanism of action	Source
Dendrophthoe falcata/carrot	Loranthaceae	Lobakmerah	Beta-amyrin, rutin acetate, beta-sitosterol	MCF-7 (*in vitro*)	Decreased in the viability of cells and exhibited by EA extract at IC_{50} 107 value of 112 μg/mL on MCF-7	[132,135]
Dendrophthoe pentandra/mistletoe	Loranthaceae	Rambut putri	Quercitrin and flavonol glycoside	T47D human ductal breast epithelial tumour	Induction of ER II (ESR2 and ER-beta) denies tyrosine kinase involvement in oncogenesis. And the expression of growth inhibition	[108,136,92]
Dillenia suffruticosa	Dilleniaceae	Simpoh air	Betulinic acid	MCF-7 (*in vitro*)	Activation of JNK1 due to DS and downregulation of ERK1, which in turn down-regulates BCL-2 to rise in the BAX/BCL-2 ratio to bring about the mitochondrial apoptotic pathway	[137]
Dysoxylum cauliflorum	Meliaceae	Dedali, langgaayer, popo kparang	Rohitukine	MCF-7, MDA 468 and MRC-5	The proliferation inhibited, and IL-2 discharge from, activated T lymphocytes, with little indication of toxicity to Jurkat E6	[138]
Echinacea angustifolia/coneflower *Etlingera elatior*/torch ginger	Asteraceae Zingiberaceae	Nenas Bunga kantan	Alkamides Quercetin	MCF-7 (*in vitro*) MCF-7 and MDA-MB-231 (*in vitro*)	Arrest of the cell cycle in the G1 phase Exhibited potent anticancer activity with IC_{50} of 173.1 and 196.2 μg/mL against MCF-7 and MDA-MB-231	[139] [41,42]
Eucheuma cottonii/Seaweed	Solieriaceae	Buaya	Catechin, rutin and quercetin	MCF-7 (*in vitro*) LA7 cells (*In vivo*)	Hormonal modulation, apoptosis induction, and oxidative status modulation. Improve oxidative status and downregulate the endogenous active estrogen biosynthesis	[43]
Eurycoma longifolia/tongkat ali	Simaroubaceae	Tongkatali	Longilactone Eurycomanol, a quassinoid	MCF-7 (*in vitro*) MCF-7 and MCF-10A (*in vitro*)	Apoptotic nuclear morphology changes such as nuclear fragmentation, hyper nuclear condensation and nuclear shrinkage Exhibits cytotoxic activity towards MCF-7 (IC_{50} =15.23±0.66μg/ml) and is less sensitive against MCF-10A (IC_{50} =66.31±0.47μg/ml)	[85,140]
Elephantopus scaber/elephant's foot	Asteraceae	Tutup bumi	Deoxyelephantopin	MCF-7 (*in vitro*)	Inhibiting growth and triggered time-dependent and dosage-dependent cell death in the MCF-7 via p53 dependent apoptotic pathway	[141]
Eupatorium odoratum/Siam weed	Asteraceae	Rumput Pahang, rumputpait	Triterpenoids, flavonoids	MDA-MB-231 (*in vitro*)	Inhibition of AKT pathways plays a role in inducing G2 arrest in MDA-MB-231 by bringing about the accumulation of inactive phospho-Cdc2 and phospho-Cdc25C, leading to subsequent G2 arrest	[142]
Ficus deltoidea/mistletoe fig	Moraceae	Mas cotek	Moretenol, quercetin-3-rutinoside	MCF-7	Inhibited cell proliferation	[71]
Garcinia mangostana/ Mangosteen	Clusiaceae	Manggis, mangusta	Mangostin	3T3 and 4T1 cells (*in vitro*)	Lipid peroxidation inhibition	[56]

(Contd...)

Table 1: *(Continued)*

Plant name/common name	Family	Local name (Malay)	Active compound	Experimental model	Mechanism of action	Source
Goniothalamus macrophyllus/airy shaw	Thymelaeaceae	Selada, selayar hitam	Styrylpyrone, goniothalaminβ-catenin	MCF-7 (*in vitro*)	Inhibited cell proliferation and markedly suppressed transcriptional activity induced by β-catenin in luciferase reporter gene assay DNA fragmentation, damage and caspase-9 activation, increase in the sub-G1 and S cell cycle phases	[72,73]
Glycine max, (soybean)	Fabaceae	Bean	Genistein and Daidzein	MCF-7 (*in vitro*)	Gene reactivation (p16, RARbeta, and MGMT), induces DNA demethylation	[30]
Gynura procumbens/longevity spinach	Steraceae	Dewa raja, Akarsebiak, Kachamakar.	SN-F11/12	MDA-MB-231 (*in vitro*)	Inhibit the development of, MDA-MB-231, at an EC_{50} value of 3.8 mg/mL. The down-regulated expression of proliferation markers, Ki67 and PCNA, and invasion markers	[143]
Hedyotis corymbosa/diamond-flower	Rubiaceae	Siku-siku, LidahUlar, Rumput Mutiara	Aspreuloside, Antimycin A3	YMB-1 breast cancer cell line	Inhibition of YMB-1 cell line with each IC_{50} value is 6.51 and 2.75 μg/mL	[144]
Hevea brasiliensis/rubber tree	Euphorbiaceae	Getah	Latex B-serum	MCF-7 (*in vitro*)	Regulate intrinsic and extrinsic apoptotic path ways in MCF-7	[103]
Hydnophytum formicarum/Caudex	Rubiaceae	Simbag hutak	7, 3′, 5′-trihydroxyflavanone (3HFD)	MCF-7 (*in vitro*)	Bring about apoptosis in MCF-7 by enhancing Bax expression stages similarly reducing the level of the anti-apoptotic protein Bcl-2 and up-regulation of pro-apoptotic Bax	[145]
Hyptis suaveolens	Lamiaceae	Lerkuing or Selasehhutan	(2E)-1- (2-hydroxy phenyl) pent-2-en-1-one (I)	MCF-7 and MDA-MB-231	Exerted inhibitory effect root extract that caused $_{50}$% inhibition (IC_{50}) was 1_{50} μg/mL and 100μg/mL, respectively, leaves and stem that caused $_{50}$% inhibition (IC_{50}) of MDA-MB- 231 was 100 μg/mL	[140,146]
Ipomoea quamoclit/morning-glory	Convolvulaceae	Kangkung	Flavonoids	MCF-7 and 3T3 cell line (in vitro)	Inhibit the proliferation, migration, and invasion of pro-metastatic and scyclooxygenase-2 (COX-2), Ipobscurine may also promote apoptosis by up-regulating pro- and also suppresses various TF. arrest at G1	[101]
Juglans regia/walnut	Juglandaceae	Melati, melor	Naphthoquinones	MDA-MB-231. (*In vitro*)	RBJR-inducing cell death by determining the appearance of Bcl-2, Bax, caspases, Tp53, Mdm-2 and TNF-α in MDA-MB-231	[47]
Labisia pumila/Kacip Fatimah	Myrsinaceae	Kacip Fatima	Alkenylresorcinols	MCF-7; MDA-MB-231. (*In vitro*)	Expression level increase in pro-apoptotic protein Bax and p53 and reduction in level expression of antiapoptotic protein BCl-2 in HM3KO, straight donating to the rise in Bax/Bcl-2 fraction	[93,147,74]
Lawsonia inermis	Lythraceae	Pacar Kuku, henna	Iaxanthone, coumarin and coumarin	MCF7 (*in vitro*)	Inhibition proliferation tumor cell with IC_{50} value of 24.85 μg/mL	[56,75,76]

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Table 1: (Continued)

Plant name/common name	Family	Local name (Malay)	Active compound	Experimental model	Mechanism of action	Source
Leea indica/Bandicoot berry	Vitaceae	Mali-mali, merbatipadang, jolok-jolok	Palmitic acid, 1-eicosanol, solanesol	MCF-7 and T47D	Inhibition of proliferation	[77,148]
Litsea garciae/Engkala	Lauraceae	Pengolaban	Alkaloid, flavonoids, chalcone	MCF-7 (*in vitro*)	Cytotoxicity activity was exhibited moderately with IC_{50} value of 73 µg/ml against MCF-7	[149]
Mangifera indica/Mango	Anacardiaceae	Mangga	Vimang, mangiferin	MCF-7 and MDA-MB-231 cell lines	Inhibiting NFjB target genes that are involved in inflammation, anti-apoptosis metastasis, and angiogenesis	[44,150]
Muntingia calabura/Calabur tree	Elaeocarpaceae	Ceri kampung	Flavonoids, tannins, saponins and steroid	MCF-7 (*in vitro*)	Inhibition of cell-survival kinase and the inflammatory TF, permeabilization of the mitochondrial membranes to cause necrotic cell death, reduction in of cells at G0/G1 phase, with an earlier increase in S and G2/M	[111]
Mangifera pajang	Anacardiaceae	Bambangan	Naringin mangiferonic acid, stigmasterol and quercitrin	MDA-MB-231 and MCF-7 (*in vitro*)	Induced cytotoxicity in the cells with IC_{50} values of 23 and 30.5 µg/ml, in MCF-7 cell cycle arrest at sub-G1 (apoptosis) phase. For MDA-MB-231 induced strong arrest in G2-M	[79,107,108]
Melastoma malabathricum	Melastomataceae	SendudukPutih	Malvidin-3,5-diglucoside	(MCF-7) *in vitro*	Inactivation of tumour suppressor genes such as p53	[151]
Morinda citrifolia/Cheese fruit	Rubiaceae	Mengkudu	Dammacanthal,	MCF7 breast cancer cells	Induced apoptosis, and expression of caspase 7 activations of p21, leading to the transcription of p53 and the Bax gene	[46]
Moringa oleifera/Drumstick	Moringaceae	Kacangkelo	Isoquercetin and astragalin	MCF-7 *in vitro*	Inhibited MCF-7 cell line with 87.13% in average at wavelength A570 nm	[45,152]
Murraya koenigii/Curry tree	Rutaceae	Daunkari, Pokokkar	Mahenine, a carbazole alkaloid, girinimbine	MCF-7 (*in vitro*)	Induce apoptosis in HL-60 and MCF-7 by down regulating survival cell of factors and distracting the cell cycle progression	[153]
Murraya paniculata/Orange Jessamine *Nephelium lappaceum*/Rambutan	Rutaceae Sapindaceae	Kemuning Rambutan	(E)-caryophyllene Trypsin and α-chymotrypsin. dithiothreitol	MCF-7 (*in vitro*) 4T1 and 3T3 cell lines	Cytotoxicity activity against MCF-7 Inhibition of proliferation and metastasis of tumors exhibited cytotoxicity (CV 40%) and 100% inhibition at a concentration of 8 µg/mL	[78] [56,154]
Nigella sativa/Black cumin	Ranunculaceae	Jintanhitam	Essential oil, thymoquinone	MCF-7 (*in vitro*)	NSEO nano emulsion induced apoptosis in MCF-7 lessens viability of the cell and alteration of nuclear morphology in a dose- and time-dependent manner	[44]
Orthosiphon stamineus/"cat whisker"	Lamiaceae	Java tea/ misaikucing	Rosmarinic acid	MCF-7 (*in vitro*)	Enhancing anti-proliferative activity of TMX against MCF-7	[155]
Pandanus amaryllifolius/Pandan leaves	Pandanaceae	Pandan wangi	Propylene glycol	MCF-7 and MDA-MB-231 (*in vitro*)	Reduced viability by inhibiting proliferation in MCF-7 and MDA-MB-231	[41]

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Table 1: (Continued)

Plant name/common name	Family	Local name (Malay)	Active compound	Experimental model	Mechanism of action	Source
Persea declinata	Lauraceae	Medanginai	α-humulene	MCF-7 (*in vitro*)	Release of higher lactate dehydrogenase and raise in ROS making, resulting in mitochondrial membrane potency perturbation, porousness of cell, and motivation of caspases-3/7	[80]
Peperomia pellucida/Pepper elder	Piperaceae	Ketumpang air	Carotol, dill apiole, pygmaein	(MCF-7) cell line (in vitro)	inhibitory concentration (IC$_{50}$) of 10.4±0.06 μg/mL	[156,157]
Phaleria macrocarpa/Crown of God	Thymelaceae	Mahkotadewa	Rutin, ferric thiocyanate and thiobarbituric acid	MCF-7 (*in vitro*)	Cytotoxic activity against MCF-7 with IC$_{50}$ between 25.5 and 40.8 μg/mL	[158]
Phyllanthus pulcher/Weed	Phyllanthaceae	Keluruttanjong, nagabuana	Triterpenoids (lupane)	MCF-7 (*in vitro*)	Exhibited cytotoxic activity, h IC$_{50}$ values ranging 7.5–13.4 μg/mL (17.1–30.5 μM)	[65]
Phyla nodiflora/matchweed	Verbenaceae	Paci-pac	Nodifloretin, larycitrin, β-sitostero	MCF-7 (*in vitro*)	Anti-proliferation and Apoptotic DNA fragmentation of MCF7 were inhibited by all the extracts with IC$_{50}$ ranging from 90 to 120 μg/mL	[100]
Physalis minima/bladder cherry	Solanaceae	Letup-letup, rumputmeranti	Withanone A, stigmasterol and withaferin A	MCF 7 *in vitro*	Anti-proliferation of NCI-H23 by apoptosis. The initiation of apoptosis was proposed to be facilitated by caspase-3, p53 and c-myc-dependent apoptosis pathways	[52,96]
Piper nigrum/black pepper	Piperaceae	Lada Hitam	Pellitorine	MCT-7 cell lines (*in vitro*)	Cytotoxic with an IC$_{50}$ value of 13.0 μg/mL	[159]
Piper betle/betel	Piperaceae	Sirih, suruh, seureuh	Catechin, morin, and quercetin	HL60 and MCF-7 cell lines	Increased in catalase activities and superoxide dismutase in the treated cells may alter the antioxidant defence system	[159]
Psidium guajava/guava	Myrtaceae.	Jambu Batu	Catechin, Rutin and Quercetin	MDA-MB-231 (*in vitro*)	Anti-proliferative activity in MDA-showed the cytotoxicity of IC$_{50}$ of 4.23 μg/mL	[117,160]
Punica granatum/pomegranate	Lythraceae	Pokok Delima	Ellagitannins	MDA-MB-231 and MCF-7 (*in vitro*)	Escalation of cancer cell adhesion and decline cancer cell migration of the MDA-MB-231 and MCF-7 also inhibit chemotaxis in cancer cell lines to SDF1α	[161]
Pueraria mirifica	Fabaceae		Daidzein	MCF-7 (*in vitro*)	Gene reactivation (p16, RARbeta, and MGMT), induces DNA demethylation	[30]
Pueraria lobata (Willdenow)	Fabaceae		Daidzein	MCF-7 (*in vitro*)	Gene reactivation (p16, RARbeta, and MGMT), induces NA demethylation	[30]
Raphanus sativus/white radish	Brassicaceae	Putih	Raphasativuside A B, phenylpropanoidsucrosides 1–7	MDA-MB-231 and MCF-7 (*in vitro*)	Cytotoxicity against all the tested cell lines, with IC$_{50}$ values from 6.71–27.92 lM.	[162]
Rhodiola rosea/golden root, rose root	Crassulaceae		Rhodioloside and salidroside	MDA-MB-231 and MCF-7 (*in vitro*)	Antiproliferation and inducing apoptotic cell death in ER-negative and ER-positive MCF-7 and MDA-MB-231	[94,86]

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Table 1: (Continued)

Plant name/common name	Family	Local name (Malay)	Active compound	Experimental model	Mechanism of action	Source
Sandoricum koetjape (Santol or cottonfruit)	Meliaceae.	Sentieh, Sento	Terpenoids	MCF-7 (*in vitro*)	Colony formation properties of MCF 7 were inhibited, induction of apoptosis machineries; stimulation of caspase 3/7 actions and A mitochondrial apoptosis pathway	[89]
Sanguinaria Canadensis (blood root)	Papaveraceae		Sanguinarine	MCF-7 (*in vitro*)	Decreases histone methylation (H3K4 and H3R17); HMTi (G9a), *in vitro* HATi and decreases histone acetylation	[30]
Scurrula ferruginea/Denser	Loranthaceae	Dapong-kahoi	Lectins	MCF-7 and MDA-MB-231 (*in vitro*)	Induction of apoptosis by morphological changes of apoptotic nuclei and DNA fragmentation and inhibited the migration and colony formation	[104,163]
Silybum marianum (milk thistle)	Asteraceae	Bungacingkeh	Silibinin	MCF-7 (*in vitro*)	Increases histone acetylation	[30]
Syzygium aromaticum/Cloves	Myrtaceae		Betulinic acid	MCF-7 (*in vitro*)	Apoptotic activation of the cell death machinery by initiating caspases 3/7 and promote chromatin condensation and nuclear break-up in the MCF-7	[63]
Sanchezia speciosa/Shrubby white vein	Acanthaceae		Quercetin	MCF-7 (*in vitro*)	Inhibition activity on HUVEC cells	[100]
Schima wallichii/Chinese guger tree	Theaceae	Gatal-gatal, Kelinchipadi	Kaempferol	MCF-7 (*in vitro*)	Antiproliferation and apoptosis by the activation of the caspase signaling cascade that includes caspase-9 and 3, and PARP	[38]
Strobilanthes crispus/black face genera	Acanthaceae	Pecahbeling	Polyphenols, catechins, caffeine	MCF-7 and MDA-MB-231 (*in vitro*)	Stimulate apoptosis and DNA division through mitochondria-dependent p53 apoptosis pathway	[41,65,164]
Tinospora crispa/Heart-leaved, Batawali	Menispermaceae	Batawali or seruntun or AkarPutarwali	Columbin, tinospora acid	MCF-7, MDA-MB-231, and 3T3 (*in vitro*)	mRNA expression levels of apoptosis-related genes (caspase-3 and caspase-9) induced by Cisplatin were significantly decreased	[165]
Trigonella foenum/Fenugreek	Fabaceae	Halba, kelabat	Diosgenin	MDA-MB-231, (*in vitro*)	Expression of pro-apoptotic genes caspase -3, caspase-8, caspase-9, p53, Fas, FADD, Bax and Bak in MCF7 were increased	[94,166]
Vernonia amygdalina /Bitter leaf	Asteraceae	Pokok South Africa	Terpenoids	MDA-MB-231 and MCF-7 (*in vitro*)	Anti-proliferation of MDA-MB-231 and MCF-7, and specific G1/S phase stimulation that arrest cell cycle in MCF-7	[109]
Thelesperma megapotamicum/Pampa tea	Asteraceae	Tetiup	Luteolin, and phenylpropanoids	MCF-7 (*in vitro*)	Inhibition in cultured MCF-7 cells	[167,168]
Theobroma cacao/Cacao tree	Malvaceae	Pokok coklat	Triterpenes, flavonoids alkaloids	MCF-7 (*in vitro*)	Anticancer activity against MCF-7 cells at (IC$_{50}$=41.4±3.3 μg/mL	[169]
Typhonium flagelliforme\Rodent tuber	Araceae	KeladiT ikus	Daukasterol	T-47d (*in vitro*)	Cytotoxicity of RTE on T47D with IC$_{50}$ value of 632μg/mL antagonistic effect by decreasing Sub-G1 RTE (63 μg/mL) and TAM 5 nM, separately from 53.19% and 44.50% to 35.86%	[170,171]

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corymbosa with IC_{50} value of 6.51 μg/mL in MCF-7 and IC_{50} value of 2.75 μg/mL in MDA-231, *Nephelium lappaceum* with 100% inhibition at IC_{50} value of 8 μg/mL, *Psidium guajava* in MDA showed the cytotoxicity of IC_{50} of 4.23 μg/mL, *Peperomia pellucida* with IC_{50} value of 10.4 μg/mL, *Phaleria macrocarpa* with IC_{50} value of 25.5–40.8 μg/mL, *Curcuma xanthorrhiza* IC_{50} value of 1.71±0.1 μg/mL, *Mangifera pajang* with IC_{50} value of 23 μg/mL in MCF-7 and IC_{50} value of 30.5 μg/mL in MDA-231 and *Phyllanthus pulcher* with IC_{50} value of 18.9±0.7 μg/mL while most of the lowest activities were found in *Etlingera elatior* with IC_{50} value of 173.1 μg/mL in MCF-7 and IC_{50} value of 196.2 μg/mL in MDA-231, *Albizia zygia* with IC_{50} value of 83.16 μg/mL, *Litsea garciae* with IC_{50} value of 73 μg/mL, *Phyla nodiflora* with IC_{50} value of 90–120 μg/mL, *Moringa oleifera* with IC_{50} value of 87.13 μg/mL, *Artocarpus altilis* exhibiting strong free radical scavenger towards DPPH with IC_{50} value of 2 μg/mL, and *Amaranthus gangeticus* with IC_{50} value of 98.8 μg/mL, *Dendrophthoe pentandra* with IC_{50} value of 107 μg/mL in MCF-7 and IC_{50} value of 112 μg/mL in MDA-231, and *Trigonella foenum* and *Theobroma cacao* with IC_{50} value of 41.4 μg/mL.

Some of the bioactive compounds that were isolated and found to be responsible for the anticancer activities from these medicinal plants that exhibited good activity are pyranocycloartobiloxanthone A (PA), dihydro-artoindonesianin C, and pyranocycloartobiloxanthone B isolated from *Artocarpus obtusus* and shows strong cytotoxic activity against MCF-7 and MDA-MB-231 with IC50 values of 5.0μg/mL in) at 30μg/mL concentartion and IC50 value of 2μg/ in *Artocarpus altilis*. Dentatin also isolated from *Clausenaex cavata* arrest MCF-7 at G0/G1 phase and ROS was significantly elevated. Moreover, dentanin (DTN) significantly blocked the induced translocation of NF-kB from the cytoplasm to the nucleus, silver nanoparticles (AgNPs) isolated from *Alternanthera tenella,* and *Coriandrum sativum* inhibited cell migration dose-dependently after 24 h of treatment. The IC_{50} value of the AgNPs was calculated to be 42.5 Lg/mL and inhibits the MCF-7 by the upregulation of the p53 tumor suppressor gene expression and the subsequent rise in expressions of pro-apoptotic proteins such as caspase-3, Bax, and caspase-9, respectively. Benzoquinonoid fraction (BQ) isolated from hexane extract of *Ardisia crispa* inhibited both COX-1 and COX-2. Amygdalin isolated from *Amaranthus lividus* activated a pro-apoptotic signalling molecule p38 mitogen-activated protein kinases (p38 MAPK) in Hs578T cells and induces apoptosis and also inhibits adhesion of breast cancer cells. Andrographolide isolated from *Andrographis paniculata* Induced apoptosis in MDA-MB-231, anti-proliferative activity by mitochondria dependent caspase mediated pathway and cell cycle arrest at G2 and M. Damnacanthal isolated from *Morinda citrifolia* induced apoptosis, and expression of caspase 7 activation of p21, leading to the tran¬scription of p53 and the Bax gene. Diallyltrisulfide isolated from *Allium sativum* stimulates the lymphocytes and macrophages that kills cancerous cells and interferes with tumor cells metabolism. Vernodalin isolated from *Centratherum anthelminticum* seeds inhibits cell growth of MCF-7 and MDA-MB-231 by induction of cell cycle arrest and apoptosis, increased of reactive oxygen species (ROS) production coupled with a downregulation of anti-apoptotic molecules (Bcl-2 and Bcl-xL) led to reduction of mitochondrial membrane potential and the release of cytochrome c from mitochondria to cytosol which triggered activation of caspase cascade, PARP cleavage, DNA damage and eventually cell death. Iaxanthone, coumarin and iacoumarin isolated from *Lawsonia inermis* Inhibites proliferation of tumor cell at IC_{50} value of 24.85μg/ml. 1'S-1'-Acetoxychavicol acetate (ACA) isolated from *Alpinia conchigera* induced cell cycle arrest at G0/G1 phase with IC_{50} values 34.0 μM to 48.0 μM. Xanthorrhizol isolated from the rhizome of *Curcuma xanthorrhiza* inhibites proliferation of MCF-7 with an EC_{50} value of 1.71μg/ml and also revealed down-regulation of the anti-apoptotic bcl-2 protein expression. longilactone isolated from *Eurycoma longifolia* exerts a strong cytotoxic activity on MCF-7 with IC_{50} of 0.53 ± 0.19 μg/ml, also induced apoptosis as evidenced by nuclear condensation, fragmentation and margination, and also shows activation of caspase-7,-8 and poly (ADP-ribose) polymerase. Eurycomanol isolated from *Eurycoma longifolia* shows cytotoxicity at IC_{50} 15.23±0.66μg/ml inMCF-7 but is less sensitive against MCF-10A with IC_{50} 66.31±0.47μg/

Table 1: (Continued)

Plant name/common name	Family	Local name (Malay)	Active compound	Experimental model	Mechanism of action	Source
Vaticadios pyroides/Thurber's Indian mallow	Dipterocarpaceae	Jankapho	Resveratrol	MCF-7 and MDA-MB-468, (*in vitro*)	Growing of MCF-7 and MDA-MB-468, on a highly active level were inhibited	[172]
Withania somnifera/Winter cherry	Solanaceae	Solok, Gelenggang	Withaferin A	ZR-75-1 (*in vitro*)	Level of lymphocyte, leukocytes, immune complexes, neutrophils, immunoglobulins (Ig) A, G and M. Significantly altered	[39,173]
Zingiber officinale/ginger	Zingiberaceae	Halia	Gingerol	MCF-7 and MDA-MB-231	Reduction in mitochondrial membrane potential. Ser-15 of p53 also phosphorylated. This increase in p53 is related to decrease of 90% in Bcl2 Inhibitor of p53, pifithrin-α, reduced the anti-cancer effects	[48,174]

AgNPs: Silver nanoparticles, EAC: Ehrlich ascites carcinoma, TF: Transcription factors

ml. Alkenylresorcinols, labisiaquinone A and labisiaquinone isolated from leaves of *Labisia pumila* exhibited strongest cytotoxic activity against MCF-7 cell line at IC_{50} values <10μm.

These plants contain other chemicals that are not isolated but rather suspected to be the principal agent for the anticancer activities these are apigenin, apigenin glycosides, luteolin, luteolin-7 glucosides, p-coumarin, lupeol, lectins, naringin, nodifloretin, β silosterol, mangiferonic acid, pellitorine, kaempferol [38], curcumin, curcuminoids, a-turmerone, [33,37,39,40], quercetin [41,42], catechin, rutin [43], xanthorrhizol [40], mangiferin [44], ferric thiocyanate, thiobarbituric acid, isoquercetin, astragalin [45], damnacanthal [46], naphthoquinones [47], triterpenoids, flavonoids, gallic acid, gingerol [48] anonaine, isolaureline, annonamine [49], xanthones [50], flavonoids, stigmasterol, carotenoids, and ascorbic acid [51], among which many are reported for their cytotoxicity and chemopreventive activity against breast cancer cell that are promising anticancer agents and has been adapted for alternative cancer therapies. Many studied plants were shown to possess variable chemical compounds that possess a tumor suppressive activities and associated with potent anticancer responses, [37,40,44,51-53]. These compounds can be considered as promising candidates for the development of novel and effective pharmaceutical agents. Studies have shown that the chances for a plant to be bioactive are significantly higher when plants' selection is done by ethnomedicinal approach as compared to random plant selection. It is anticipated that the present review can be used to validate ethnomedicinal practices and bioactivities of these plants.

Anticancer mechanism

1. Inhibition of lipid peroxidation as exhibited by *Garcinia mongostana* [54], *Alstonia scholaris* [55, 56] and *Annona muricata* [49, 57, 58].
2. Scavenging reactive oxygen species (ROS) as shown by *Abrus agglutinin* and *Allium sativum* [59, 60] and normalize n (AFP) levels in *Allium sativum* [33].
3. Inhibiting proliferation via the activation of caspase-3 and caspase-9, up-regulation of the ratio of bax/bcl-2 protein expression in *Ardisia brevicaulis* [61] *Artocarpus obtusus* [50, 62] *Ardisia brecaulis* [63], *Carica papaya* [64] *Catharanthus roseus* [118-119], *Costus speciosus* [121-122], *Cucuma zedoaria* [65], *Dysoxylum cauliforum* [66], *Goniosthalamus macrophyllus* [137-138], *Gynura procumbens* [139], *Lawsonia inermis* [56,146-147], *Leea indica* [148-149], *Nepthelium lappaceum* [56,156] *Pandanus amarylfolius* [41], *Phyla nodiflora* [67], *Physalis minima* [52, 78], *Rhodiola rosea* [68], *Vernonia amygdalina* [65] and *Schima wallichi* [38].
4. Induced mitochondrial and nuclear DNA damage like in C*urcuma longa* [33, 37].
5. Organelle organisation alteration, cellular plan and differentiation degree of cellular metabolism in *Azadirachta indica* [65].
6. Increase histone acetylation like in *Allium cepa* [60].
7. Declined in polymorphonuclear leukocyte infiltration and migration, reduced primary antibody synthesis and nearly inhibited the classical complement pathway like in *Boswellia serrate* [69, 70].
8. Cell morphological changes such as cytoplasmic shrinkage, condensation of nucleus and formation of membrane-bound vesicles in *Abrus precatorius* [59, 71] and *Scurrula ferruginea* [88, 166].
9. Expression levels of apoptosis-related genes (caspase-3 and caspase-9) *Tinospora crispa* [72], *Andrographis panniculata* [67, 101-102], *Brassica oleraceae* [63, 80, 111], *Curcuma xanthorrhiza* [73], *Eucheuma cottonii* [66].

Anticancer drugs destroy cancer cells by stopping growth or multiplication at some point in their life cycle. This paper has shown that the cytotoxicity of plants that downregulate the anti-apoptotic genes such as Bax/Bcl2 (apoptosis inducing genes) that promote cell death, like in *Artocarpus obtusus* [50], rise in Bax/Bcl2 ratio to induce apoptotic pathway like in *Dillena suffruticosa* [74] also in *Z. offinalis* [48], Juglans regia [47], *L. pumila* [75] and *T. foenum* [76] and on the other hand, the use of pro-apoptic genes like caspases, 3, 7, 8

and 9, and P53 has make a clear expression in in *Artocarpus obtusus* [50], *C. sativum* [95], *G. macrophyllus* [91], *Persea declinata* [80], *P. minima* [96], *Sandoricum koetjape* [89], *T. foenum* [94], *S. wallichii* [38], and *Brassica oleracea* [97]. Apoptosis and cell proliferation were the major biological pathway in cell death, and plant with highest apoptosis were *A. sativum* [33,60], *C. sativum* [98], *Anisochilus carnosus, P. minima* [52,96], *Sandoricum koetjape* [89], *E. cottonii* [43], *C. xanthorrhiza* [40], *Nigella sativa* [99], *R. rosea* [94], *Sanchezia speciosa* [100], *and Ipomoea quamoclit* [101], and those with least apoptosis were *Phyla nodiflora* [102], *Brassica olorecea* [97], *Murraya koenigii* [42], and *Hydnophytum formicarum* [103] while those plant that shows apoptosis with morphological changes includes *E. longifolia* [85], *S. ferruginea* [104], *Syzygium aromaticum* [63], *C. longa* [33,37], *A. precatorius* [59], and *C. anthelminticum* [105], and in cell cycle arrest, *C. sativum, A. paniculata,* and *M. pajang* arrest was made at G2/M [81,98,106,107], respectively, while arrest at S-phase was seen in *Alpinia officinarum* [108], sub-G1/S in *Vernonia amygdalina* [109], and reduction in G0/G1 phase with earlier increase in S and G2/M was observed in *A. conchigera* [110] and *Muntingia calabura* [111]. Finally, on the cell line used, almost all the plants were used against either MCF-7 or MDA-MB-231 or both.

Although the clinical trials showed that herbs were helpful against cancer, these outcomes require further confirmation with rigorously controlled trials, and many clinical trials focusing on the anticancer effects of herbal formulas have been conducted. Although many of them demonstrated that medicinal plants are helpful against cancer, especially useful in improving survival and quality of life in patients suffering from advanced cancer, the lack of controls and reporting bias have been severe flaws [33].

The information presented in this review aim at providing a general outline or descriptions of what type of mechanisms do plant extracts to inhibit cancer and also deliver therapeutic prove for some of the conventionally utilized anticancer plants. The pharmacological report advocates that these traditional practices are connected to the presence of dynamic compounds with anticancer potentials. Dissimilar plants have been found fighting against diverse cell lines of cancer even though this review only targets BC, pure chemical constituents have likewise been separated from these plants and established very active, still few numbers of pharmacological, phytochemical, and ethnomedicinal, examinations have been fully recognized on majority of these plants. Evidently, it is the time to lay more emphasis on scientific investigations on medicinal plants.

Anticancer drug suffers from generally inadequate efficacy and number of serious adverse effects in human health. These plants are commonly used in the conventional system of medicines in breast cancer remedies. Several reported works conclude that medicinal plants possess anticancer activities by the virtue of their active compounds, and *in vivo* and *in vitro* induced cancers are proved with scientific principles to ameliorate the cancers with use of these plant extracts. Introduction of apoptosis in cells *in vitro* can be done through different patterns. The typical systems are the disclosure of thymocytes to glucocorticoids. Other practices consist of DNA damage either by irradiation, exposure to drugs that prevent trypsin, topoisomerase, withdrawal of advance factors from growth media, cell cycle perturbation, exposure to inhibitors/activators of kinases or phosphatases, interloping with Ca2+ homeostasis, over the appearance of p53 adherents of Ced-3/ICE and so on.

CONCLUSION

Throughout the world, especially developing and under-developing countries, plants have been exploited as medicine to meet primary healthcare needs. There has been a great switchover in the universal trend of medicine selection from synthetic to herbal medicine, which indicates "Return to Nature." Medicinal plants have been best known for millennial and are highly important all over the world as a rich source of therapeutic agents. It is estimated that vast majority of the population

relies on medicinal plants for therapy against several diseases or disorders [174,175].

A large number of novel anticancer drugs have been discovered from natural products in the past, and new ones are continually being developed; many plant species are still used by herbalists and traditional practitioner healers in Malaysia for treating breast cancer, considering the number of new cases in breast cancer and rising epidemiology in Malaysia. This review reports the investigations of many researchers on natural plants in breast cancer medication in Malaysia that inhibited cell growth in both *in vitro* and *in vivo* anticancer activities. However, plants from a good number of families have never been investigated phytochemically to reveal their active compound as well as their mechanism of action. These include Zingiberaceae, Asteraceae, Fabaceae, Loranthaceae, Meliaceae, Moraceae, Amaranthaceae, Araceae, Solanaceae, Annonaceae, Acanthaceae, Apocynaceae, Liliaceae, Rubiaceae, Apiaceae, Lauraceae, and Piperaceae (in order of appearance) which have diverse uses in traditional medicine, some of the phytochemicals with potency includes Anonaine, Atisine, genistein, glistein, ritun, pymaein, antimycin, aspreuloside, calotoxin, calotropin, bauhinoxepin, bauhiniastatins, caratol, and xanthorrhizol, and apoptosis and cell proliferation were the major biological pathway in cell death [33,37,39,40] in MCF-7 and MDA-231 cell lines. The present study calls for further research aimed at isolating the bioactive compounds responsible for the observed activity, and also, toxicology of these plants also needs to be studied in details and also points out their clinical trials. These compounds could serve as novel supports in search for new drugs.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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