INTRODUCTION

Cancer

Cancer is a group of diseases characterized by abnormal cell growth with the potential to affect 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, dox, gemcitabine, mitoxantrone, and ixabepilone.

Cell cancer resistance to chemotherapy is still a heavy burden that impacts 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, Nagaprasanthi et al. [25] reviewed 56 important ethnomedical 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] and reviewed reports 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 [26]. 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 IC₅₀ 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.

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 ERs and other RE. The non-nuclear/nongenomic activity can also be activated by tamoxifen and enhanced in the presence of overexpression and hyperactivation of RTKs and can contribute to endocrine therapy resistance. Overall, the nuclear/genomic and non-nuclear/nongenomic 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 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 folkloric 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 IC₅₀ value of 10 μg/mL, Bauhinia purpurea with IC₅₀ value of 9 μg/mL for MCF-7 and IC₅₀ value of 17 μg/mL for MDA-231, Coleus forskohlii extract with IC₅₀ value of 1.3 μg/mL for MCF-7 and IC₅₀ value of 3.3 μg/mL for MDA-231, Piper nigrum with IC₅₀ value of 13 μg/mL, Casearia capitellata with IC₅₀ value of 2 μg/mL in MCF-7, Hedystis

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 the output of immunoglobulin, M1Leukin2, 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 quality of platelets and leukocytes through motivating the hemopoietic role, encouraging the opposite transformation from tumor cells into regular cells, helping metabolism and avverting 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 at all stages of breast cancer. Recent studies shows that tamoxifen and the new pure antiestrogens appear to have different mechanistic 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 metabolic potential of a tumor [34,35].
| 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     | Pukullima           | Budmunchiamines A, B, and C            | MCF-7 (in vitro)         | Cytotoxic to MCF-7 at IC<sub>50</sub> values of 83.16 µg/mL and 57.54 µg/mL         | [112,113]           |
| Allium cepa (Onion)     | Liliaceae       | Bawang putih       | Diallyl trisulfide                     | MCF-7 (in vitro)         | Increase histone acetylation                                                        | [30]                 |
| Allium sativum/garlic   | Liliaceae       |                    | 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 | [30,52,33,60]       |
| 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<sub>50</sub> 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 24 h of treatment. The IC<sub>50</sub> value of 42.51 g/mL. The AgNPs showed a significant reduction in the migration of MCF-7 cells Reduce the tumor multiplicity incidence, decline in the glutathione levels and increased the lipid peroxidation | [115]               |
| Alistonia scholaris/blackboard/scholar tree | Apocynaceae | Pulalillin          | Alstonine, ditamine, echitenine, and vilialstonine | EAC (in vitro)          | Inhibiting peroxidation of phosphatidylincholine liposomes permased with Fe<sup>3+</sup>/ ascorbate to scavenge ABTS, DPPH and hydroxyl radicals, to lessen Fe (III) to Fe (II) and to chelate Fe (II) | [54,55]          |
| Amaranthus lividus/slender amaranth | Amaranthaceae | Bayamhijau         | β-carotene and amygdalin               | MCF7 and MDA-MB-231 (in vitro) | Antiproliferation of MCF-7 at IC<sub>50</sub> values of 98.8 µg/mL | [58,87]           |
| Amaranthus gangeticus/red spinach | Amaranthaceae | Ayam Merah          | Carotenoids and ascorbic acid          | MCF-7 (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]       |
| Andrographis paniculata/green chirayta | Acanthaceae   | Hemptedu Bumi      | Andrographolide, diterpene lactone    | MDA-MB-231 (in vitro)    | 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]        |
| Ardisia crispa/Christmas berry | Myrsinaceae    | Mata Ayam           | Benzoquinonoid, α-β-amyrin, and Ardisiacrispin A | MCF7 (in vivo)           |                                          |                     |

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

(Contd...)
| Plant name/common name | Family | Active compound | Experimental model | Mechanism of action | Source |
|------------------------|--------|-----------------|--------------------|--------------------|--------|
| **Annona muricata**/Soursop | Annonaceae | Anonaine, isolaureline, annonamine | MCF-7 (in vitro) | Anti-proliferation activity | [49,57] |
| **Annona squamosa**/sugar apple | Annonaceae | Atisine, oxophoebine, and reticuline | MCF-7 (in vitro) | Anti-proliferation activity | [119,120] |
| **Ardisia brevicaulis**/coralberry or marlberry | Myrsinaceae | 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); inhibits HMTi (G9a), HATi and decreases histone acetylation | [30] |
| **Artocarpus altilis**/breadfruit | Moraceae | Pyranocycloartobiloxanthone A, and B dihydro-artoindonesianin C, | MCF-7 (in vitro) | Exhibiting strong free radical scavenger towards DPPH with IC<sub>50</sub> value of 2 µg/mL with prominent discoloration | [121,122] |
| **Artocarpus obtusus**/breadfruit | Moraceae | Pyranocycloartobiloxanthone A | MCF-7 (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 | Azadirachtin, limonoid | MCF-7 (in vitro) | Organelle organization alteration, cellular plan, and differentiation degree, cellular metabolism and differentiation degree, cellular metabolism | [69] |
| **Bauhinia purpurea**/butterfly tree | Fabaceae | Bauhiniastatins, lutein, and B-sitosterolbauhinoxepin | MCF-7 and MDA-MB 231 (in vitro) | Active against MCF-7 at (IC<sub>50</sub> ≈ 9 µg/mL), and MDA-MB 231 at IC<sub>50</sub> ≈ 17 µg/mL | [123,90] |
| **Brassica oleracea**/cabbage | Brassicaceae | β-carotene, lutein, α-Tocopherol | 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 | Boswellic acid | MCF-7 (in vitro) | Declined in polymorphonuclear leukocyte infiltration and migration, reduced primary antibody synthesis and nearly inhibited the classical complement pathway mediated signal transduction | [82,83] |
| **Clausena excavata** | Rutaceae | Dentatin | MCF-7 (in vitro) | DTN treatment significantly arrested MCF-7 cells at the G0/G1 phase (p<0.05), and ROS was significantly elevated. Moreover, DTN significantly blocked the induced translocation of NF-κB from the cytoplasm to the nucleus | [125] |
| **Calotropis gigantea**/crown flower | Apocynaceae | Calotropin, frugoside, calotoxin | MCF-7 and MDA-MB-231 (in vitro) | Inhibited MCF-7 and MDA MB-231 cells, IC<sub>50</sub> of DCM extract with IC<sub>50</sub> values ranging from 1.3 to 3.3 µg/mL | [126] |
| **Capsicum annuum**/red chilli | Solanaceae | Capsaicin, myricetin; a bioflavonoid | MCF-7 (in vitro) | Hindering production in LPS-stimulated RAW 264.7 macrophages | [127,128] |
| 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 Exhibited by EA extract at IC_{50} value of 2 µg/mL on MCF-7 inhibiting the proliferation of the Jurkat cell line and promoting the growth of PBMCs | [129]  |
| *Casearia capillata*   | Flacourtiaceae     | Similit Matangi    | Genistein, glicistein, glycoside                      | MCF-7 (In vitro)                        | Induced apoptosis marked by cell size shrinkage, deformed cytoskeletal structure and DNA fragmentation Antioxidant enzymes were disturbed leading to H_{2}O_{2} rise; arrest made at the G2/M and apoptosis by the death receptor and mitochondrial pathways 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 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 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 | [65]   |
| *Catharanthus roseus*  | Apocynaceae        | KemuntingCina.     | Vinblastine and vincristine                           | Jurkat cell line (In vitro)             |                                                                                      | [66,98]|
| *Centratherum anthelminticum/black cumin* | Asteraceae | Kalajiri, somraj.  | Vernodalin                                            | MCF-7 and MDA-MB-231 (In vitro)         | Induced apoptosis marked by cell size shrinkage, deformed cytoskeletal structure and DNA fragmentation Antioxidant enzymes were disturbed leading to H_{2}O_{2} rise; arrest made at the G2/M and apoptosis by the death receptor and mitochondrial pathways 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 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 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 | [105]  |
| *Coriandrum sativum*   | Apiaceae           | Ketumbar           | αpinene, limpene, γ-terpinene, p-cymene              | MCF-7 (In vitro)                        | Antioxidant enzymes were disturbed leading to H_{2}O_{2} rise; arrest made at the G2/M and apoptosis by the death receptor and mitochondrial pathways 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 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 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 | [67]   |
| *Curcuma longa/Turmeric* | Zingiberaceae       | Kunyit              | α-Turmerone, curcuminoids and curcumin in curcumin    | MCF-7 and MDA-MB-231 (In vitro)         | Decreases histone and protein acetylation increases histone acetylation, reduces expression of several HDACs sequence-specific demethylation at promoter regions of epigenetically silenced genes 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 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 | [30,33,37]|
| *Coriandrum sativum/coriander* | Apiaceae | Ketumbar           | Flavonoids                                            | MCF-7 (In vitro)                        |                                                                                      | [95]   |
| *Cheilocostus speciosus/crepe ginger* | Costaceae | SetawarHutan       | Costunolide                                           | MCF-7 AND MDA-MB-231 (In vitro)         |                                                                                      | [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 Expression of hTERT mRNAs and not hTER were inhibited | [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 Anti-proliferation in MCF-7, HCT-116 and Ca Ski                                                                 | [40]   |
| *Curcuma zedoaria*      | Zingiberaceae      | Temuhitam          | Alismol and curzerenone                               | MCF-7 (In vitro)                        | Anti-proliferation in MCF-7, HCT-116 and Ca Ski                                                                                           | [134]   |

(Contd...)
| Plant name/common name          | Family          | Local name (Malay) | Active compound                  | Experimental model | Mechanism of action                                                                 |
|--------------------------------|-----------------|-------------------|----------------------------------|--------------------|-------------------------------------------------------------------------------------|
| Dendrophthoe falcata/carrot     | Loranthaceae    | Lobakmerah        | Beta-amyrin, rutin acetate, beta-sitosterol | MCF-7 (in vitro)   | Decreased in the viability of cells and exhibited an IC<sub>50</sub> value of 11.2 µg/mL on MCF-7 due to down-regulation of ER expression leading to Akt down-regulation, cell cycle arrest, and cell death |
| Dendrophthoe pentandra/mistletoe| Loranthaceae    | Rambut putri      | Quercitrin and flavonol glycoside | T47D human ductal breast epithelial tumour (in vitro) | Induction of ER II (ESR2 and ER-beta) by EA extract at IC<sub>50</sub> value of 112 µg/mL on MCF-7 and inhibition of cell proliferation |
| Dillenia suffruticosa/simpoh air| Dilleniaceae    | Simpoh air        | Betulinic acid                   | MCF-7, MDA-468 and MRC-5 | Activation of JNK1 due to DS and down-regulation of ERK1, which in turn down-regulates BCL-2 to bring about the mitochondrial apoptotic pathway. |
| Dysoxylum cauliflorum/dedali, langgaayer, popo kparang| 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 |
| Echinacea angustifolia/coneflower| Asteraceae | Nenas             | Alkamides                        | MCF-7 (in vitro)   | Arrest of the cell cycle in the G1 phase |
| Etlingera elatior/torch ginger  | Zingiberaceae   | Bunga kantan      | Quercetin                         | MCF-7 and MDA-MB-231 (in vitro) | Exhibited potent anticancer activity with IC<sub>50</sub> values of 173, 1562, and 1962 µg/mL against MCF-7 and MDA-MB-231. |
| Eucheuma cottonii/buaya | Solieriaceae    | Buaya              | Catechin, rutin and quercetin    | MCF-7 (in vitro)   | Hormonal modulation, apoptosis induction, and oxidative status modulation. Improve oxidative status and downregulate the endogenous active estrogen biosynthesis |
| Eurycoma longifolia/tongkat ali| Simaroubaceae   | Tongkatali         | Longilactone, a quassinoid        | MCF-7 (in vitro)   | Apoptotic nuclear morphology changes such as nuclear fragmentation, hyper nuclear condensation and nuclear shrinkage |
| Elephantopus scaber/tutup bumi| Asteraceae      | Tutup bumi        | Deoxyelephantopin                 | MCF-7 (in vitro)   | Inhibiting growth and triggered time- and dosage-dependent cell death in the MCF-7 via p53 dependent apoptotic pathway. |
| Eupatorium odoratum/Siam weed   | Asteraceae      | Rumput Pahang, rumput | Triterpenoids, flavonoids       | MDA-MB-231 (in vitro) | Inhibition of AKT pathway plays a role in inducing G2 arrest in MDA-MB-231 by bringing about the accumulation of inactive phospho-Cdc2 and phosphorylated G2 arrest markers, leading to subsequent G2 arrest |
| Euphorbia longifolia/tongkat ali| Asteraceae      | Euphorbiomal, a quassiod | Triterpenoids, flavonoids       | MCF-7 (in vitro)   | Inhibitory activity towards MCF-7 and is less sensitive against MCF-10A, MDA-MB-231, and MDA-MB-468. |
| Fixea delavayi/mistleke Fig   | Moraceae        | Mas cotek         | Methyl-3,4-dihydroxyphenylethanol | MCF-7 (in vitro)   | Induced G2 arrest in MDA-MB-231 and MCF-7 by bringing about the accumulation of inactive phospho-Cdc2 and phospho-AKTAktC, leading to subsequent G2 arrest |
| Garcinia mangostana/mangosteen | Clusiaceae      | Mangostin         | Mangostin                         | 3T3 and 4T1 cells (in vitro) | Lipid peroxidation inhibition |

Table 1: (Continued)
| Plant name/common name                  | Family          | Local name (Malay) | Active compound                           | Experimental model | Mechanism of action                                                                                                                                                                                                 | Source |
|----------------------------------------|-----------------|-------------------|-------------------------------------------|--------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|
| *Goniothalamus macrophyllus* / airy    | Thymelaeaceae   | Selada, selayar    | 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)* | Gen reactivation (p16, RARbeta, and MGMT), induces DNA demethylation                                                                                                                                                  | [30]   |
| *Gymnura 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<sub>50</sub> 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, LihabUlar, Rumpit Mutiara | Aspreuloside, Antimycin A3              | YMB-1 breast cancer cell line | Inhibition of YMB-1 cell line with each IC<sub>50</sub> 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       | (2E)-1- (2-hydroxy phenyl) pent-2-en-1-one (I) | MCF-7 and MDA-MB-231 | Exerted inhibitory effect root extract that caused <sub>50</sub>% inhibition (IC<sub>50</sub>) was 1.9 µg/mL and 100 µg/mL respectively, leaves and stem that caused <sub>50</sub>% inhibition (IC<sub>50</sub>) 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 cyclooxygenase-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)* | RBBR-inducing cell death by determining the appearance of Bcl-2, Bax, caspases, Tp53, Mdm-2 and TNF-a in MDA-MB-231 Expression level increase in pro-apoptotic protein Bax and p53 and reduction in level expression of antiapoptotic protein BCl-2 in HM3K0, straight donating to the rise in Bax/Bcl-2 fraction | [47]   |
| *Labisia pumila* / Kacip Fatimah       | Myrsinaceae     | Kacip Fatima      | Allkenylresorcinols                       | 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 HM3K0, straight donating to the rise in Bax/Bcl-2 fraction | [93,147,74]|
| *Lawsonia inermis*                     | Lythraceae      | Pacar Kuku, henna | Ixanthonone, coumarin and coumarin         | MCF7 *(in vitro)* | Inhibition proliferation tumor cell with IC<sub>50</sub> value of 24.85 µg/mL                                                                                             | [56,75,76]|

Table 1: *(Continued)*
| Plant name/common name | Active compound | Family | Local name | Experimental model | Mechanism of action | Source |
|-----------------------|----------------|--------|------------|--------------------|---------------------|--------|
| Leea indica/Bandicoot berry | Palmitic acid, 1-eicosanol, solanesol | Vitaceae | Mali-mali, merbatipadang, jolok-jolok | MCF-7 and MDA-MB-231 cell lines | Inhibition of proliferation | [149] |
| Litsea garciae/Engkala | Alkaloid, flavonoids, chalcone | Lauraceae | Pengolaban | MCF-7 (in vitro) | Cytotoxicity activity was exhibited moderately with IC₅₀ value of 73 µg/ml in MCF-7 cell phase. For MDA-MB-231 induced strong arrest | [149] |
| Mangifera indica/Mango | Vimang, mangiferin | Anacardiaceae | Mangga | MCF-7 and MDA-MB-231 cell lines | Inhibiting NFjB target genes that are involved in inflammation, anti-apoptosis, metastasis, and angiogenesis | [44] |
| Muntingia calabura/Calabur tree | Flavonoids, tannins, saponins and steroid | Elaeocarpaceae | Cerkapung | MCF-7 (in vitro) | Inhibition of cell-survival kinase and the inflammatory TF, permeabilization of the mitochondrial membranes to cause necrotic cell death, induction of apoptosis and down-regulation of cell cycle proteins | [111] |
| Mangifera pajang | Naringin mangiferonic acid, stigmasterol and quercitrin | Anacardiaceae | Bambangan | MDA-MB-231 and MCF-7 (in vitro) | Induced cytotoxicity in the cells with IC₅₀ 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 | [79,107,108] |
| Melastoma malabathricum/Rambutan | Malvidin-3,5-diglucoside | Melastomataceae | Senduduk Putih | MCF-7 (in vitro) | Inactivation of tumour suppressor genes such as p53 | [151] |
| Morinda citrifolia/Cheese fruit | Damnacanthal, | Rubiaceae | Mengkudu | MCF-7 breast cancer cells | Induced apoptosis, and expression of caspase 7 activations of p21, leading to the transcription of p53 gene and the Bax gene in average at wavelength A570 nm | [46] |
| Moringa oleifera/Drumstick | Isoquercetin and astragalin | Moringaceae | Kacangkelo | MCF-7 (in vitro) | Inhibited MCF-7 cell line with 87.13% in average at wavelength A570 nm | [45,152] |
| Murraya koenigii/Curry tree | Mahenine, a carbazole alkaloid, girinimbine | Rutaceae | Daunkari, Pokok kar | 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 | (E)-caryophyllene | Rutaceae | Kemuning | MCF-7 (in vitro) | Cytotoxicity activity against MCF-7 and MDA-MB-231 cell lines | [78] |
| Nephelium lappaceum/Rambutan | Trypsin and α-chymotrypsin, dithiothreitol | Sapindaceae | Rambutan | 4T1 and 3T3 cell lines | Inhibition of proliferation and metastasis of tumors exhibited cytotoxicity (CV 40%) and 100% inhibition at a concentration of 8 µg/mL | [56,154] |
| Nigella sativa/Black cumin | Essential oil, thymoquinone | Ranunculaceae | Jintan hitam | 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" | Rosmarinic acid | Lamiaceae | Java tea/misaikucing | MCF-7 (in vitro) | Enhancing anti-proliferative activity of MSCE against MCF-7 and MDA-MB-231 cell lines | [155] |
| Pandanus amarylfolius/Pandan leaves | Propylene glycol | Pandanaceae | Pandan wangi | MCF-7 and MDA-MB-231 (in vitro) | Reduced viability by inhibiting proliferation in MCF-7 and MDA-MB-231 | [41] |
| 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  | [80]         |
|                        |                       |                    |                 |                    | perturbation, porousness of cell, and motivation of caspases-3/7 inhibitory concentration (IC<sub>50</sub>) of 10.4±0.06 µg/mL |              |
| Peperomia pellucida /Pepper elder | Piperaceae | Keturumpang air    | Carotol, dill apiole, pygmaein | (MCF-7) cell line  | Cytotoxic activity against MCF-7 with IC<sub>50</sub> between 2.55 and 408 µg/mL                    | [156,157]    |
| Phaleria macrocarpa/Crown of God | Thymelaceae | Mahkotadewa        | Rutin, ferri thiocyanate and thiobarbituric acid | MCF-7 (in vitro) | Exhibited cytotoxic activity, h IC<sub>50</sub> values ranging 7.5-13.4 µg/mL (171-30.5 µM) | [158]        |
| Phyllanthus pulcher/Weed | Phyllanthaceae        | Kelurutanjong, nagabuana | Trriterpenoids (lupane) | MCF-7 (in vitro) | Anti-proliferation and Apoptotic DNA fragmentation of MCF7 were inhibited by all the extracts with IC<sub>50</sub> 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      | MCF-7 cell lines  | Cytotoxic with an IC<sub>50</sub> value of 13.0 µg/mL                                               | [159]        |
| Piper betle/betel      | Piperaceae             | Sirih, suruh, seureuh | Catechin, morin, and quercitin | (HL60 and MCF-7) | 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<sub>50</sub> of 4.23 µg/mL                | [117,160]    |
| Punica granatum/pomegranate | Lythraceae | Pokok Delima       | Ellagittannins   | MDA-MB-231 (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, phenylpropanoidesucrosides 1–7 | MDA-MB-231 and MCF-7 (in vitro) | Cytotoxicity against all the tested cell lines, with IC<sub>50</sub> values from 6.71-27.92 µM | [162]        |
| Rhodola 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]      |
| Plant name/common name | Local name (Malay) | Active compound | Experimental model | Mechanism of action | Source |
|------------------------|-------------------|-----------------|-------------------|-------------------|--------|
| *Sandoricum koetjape* (Santal or cottonfruit) | 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) | Papaveracea | Sanguinarine | MCF-7 (*in vitro*) | Decreases histone methylation (H3K4 and H3R17); HMTi (G9a), *in vitro* HATi and decreases histone acetylation. Induction of apoptosis by morphological changes of apoptotic nuclei and DNA fragmentation and inhibited the migration and colony formation | [30] |
| *Scurrula ferruginea/Denser* | 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) | Bungacingkeh | Silibinin | MCF-7 (*in vitro*) | Increases histone acetylation | [30] |
| *Syzygium aromaticum*/ Cloves | Kaempferol | 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* | Quercetin | | MCF-7 (*in vitro*) | Inhibition activity on HUVEC cells | [100] |
| *Schima wallichii*/Chinese guger tree | Pecahbeling | Polyphenols, catechins, caffeine | MCF-7 and MDA-MB-231 (*in vitro*) | Stimulate apoptosis and DNA division through mitochondria-dependent p53 apoptosis pathway mRNA expression levels of apoptosis-related genes (caspase-3 and caspase-9) induced by Cisplatin were significantly decreased | [41,65,164] |
| *Strobilanthes crispus/black face genera* | Columbin, tinospora acid | | | | |
| *Tinospora crispa*/Heart-leaved, Batawali | MCF-7, MDA-MB-231, and 3T3 (*in vitro*) | | | | |
| *Trigonella foenum*/Fenugreek | Diosgenin | | | | |
| *Vernonia amygdalina*/Bitter leaf | Pokok South Africa | Terpenoids | MDA-MB-231, MCF-7 and 3T3 (*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] |
| *Thelesperma megapotamicum*/Pampa tea | Pokok coklat | Triterpenes, flavonoids, alkaloids, Daukasterol | MCF-7 (*in vitro*) | Anticancer activity against MCF-7 cells at (IC<sub>50</sub> = 41.4±3.3 µg/mL) Cytotoxicity of RTE on T47D with IC<sub>50</sub> 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% | [167,168] |
| *Theobroma cacao*/Cacao tree | KeladiTikus | | T-47d (*in vitro*) | | [169] |
| *Typhonium flagelliforme*/Rodent tuber | | | | | [170,171] |

(Contd...)
with IC\textsubscript{50} value of 6.51 µg/mL in MCF-7 and IC\textsubscript{50} value of 2.75 µg/mL in MDA-231. Nephelium lappaceum with 100% inhibition at IC\textsubscript{50} value of 8 µg/mL. *Psidium guajava* in MDA showed the cytotoxicity of IC\textsubscript{50} of 4.23 µg/mL. *Peperomia pellucida* with IC\textsubscript{50} value of 10.4 µg/mL. *Phaleria macrocarpa* with IC\textsubscript{50} value of 25.5–40.8 µg/mL. *Curcuma xanthorrhiza* IC\textsubscript{50} value of 1.71±0.1 µg/mL. *Mangifera pajang* with IC\textsubscript{50} value of 23 µg/mL in MCF-7 and IC\textsubscript{50} value of 30.5 µg/mL in MDA-231. *Phyllanthus acidus* with IC\textsubscript{50} value of 18.9±0.7 µg/mL while most of the lowest activities were found in *Etinglera elatior* with IC\textsubscript{50} value of 173.1 µg/mL in MCF-7 and IC\textsubscript{50} value of 196.2 µg/mL in MDA-231. *Albizia zygia* with IC\textsubscript{50} value of 83.16 µg/mL. *Litsea garciae* with IC\textsubscript{50} value of 75 µg/mL. *Phyla nodiflora* with IC\textsubscript{50} value of 90–120 µg/mL. *Moringa oleifera* with IC\textsubscript{50} value of 87.13 µg/mL. *Artocarpus altilis* exhibiting strong free radical scavenger towards DPPH with IC\textsubscript{50} value of 2 µg/mL. *Amaranthus gangeticus* with IC\textsubscript{50} value of 98.0 µg/mL. *Bendrothax pentandra* with IC\textsubscript{50} value of 107 µg/mL in MCF-7 and IC\textsubscript{50} value of 112 µg/mL in MDA-231. *Trigonella foenum* and *Theobroma cacao* with IC\textsubscript{50} value of 41.4 µg/mL.

Some of the bioactive compounds that were isolated and found to be responsible for the anticanter activities from these medicinal plants that exhibited good activity are pyran-cycloartobiliosanthe A (PA), dihydroartiodonesianin C, and pyranocycloartibolisanthe B isolated from *Artocarpus abatus* and shows strong cytotoxic activity against MCF-7 and MDA-MB-231 with IC\textsubscript{50} values of 5.0µg/mL. *Curcuma xanthorrhiza* in vitro concentration and IC\textsubscript{50} value of 2.0 µg/mL. *Withania somnifera* with IC\textsubscript{50} value of 1.71±0.1 µg/mL. Dentatin also isolated from *Clausena cava* arrest MCF-7 at 60/ G1 phase and ROS was significantly elevated. Moreover, dentatin (DTN) significantly blocked the induced translocation of NF-κB 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\textsubscript{50} value of the AgNPs was calculated to be 42.5µg/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 *Alternanthera crispa* inhibited both COX-1 and COX-2. Amygdalin isolated from *Aranthasus 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 transcription 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 *Centractrum anthemisicum* 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. Javanthren, coumarin and tacomanin isolated from *Lavesona inermis* Inhibites proliferation of tumor cell at IC\textsubscript{50} value of 2.485±0.5 µg/mL 1′-Acetoxychavicol acetae (ACGA) isolated from *Alpinia cngiuga* induced cell cycle arrest at G0/G1 phase with IC\textsubscript{50} values 34.0 µM to 48.0 µM. Xanthonrhizol isolated from the rizome of *Curcuma xanthorrhiza* inhibites proliferation of MCF-7 with an IC\textsubscript{50} value of 1.71 µg/mL and also revealed down-regulation of the anti-apoptotic bcl-2 protein expression. Loniglic tone isolated from *Eurycoma longifolia* exerts a strong cytotoxic activity on MCF-7 with IC\textsubscript{50} of 0.53 ± 0.19 µg/mL, also induced apoptosis as evidenced by nuclear condensation, fragmentation and margination, and also showsactivation of caspase-7, -9 and poly (ADP-ribose) polymerase. Eurycomanone isolated from *Eurycoma longifolia* shows cytotoxicity at IC\textsubscript{50} 15.2±6.2 µg/mL inMCF-7 but is less sensitive against MCF-10A with IC\textsubscript{50} 66.3±0.47 µg/
ml. Alkenylresorcorins, labisaquinone A and labisaquinone isolated from leaves of *Labisia pumila* exhibited strongest cytotoxic activity against MCF-7 cell line at IC₅₀ 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, nodiflorin, β-sitosterol, mangiferonic acid, peltorine, kaempferol [38], curcumin, curcuminoids, α-tumerone, [33,37,39,40], queretin [41,42], catechin, rutin [43], xanthorrhizol [40], mangiferin [44], ferraricholic acid, thioharbarbituric acid, isoaquarine, astraquin [45], damacanthal [46], naphthoquinones [47], triterpenoids, flavonoids, gallic acid, gingerol [48] annonaine, isoaquarine, annonamine [49], xanthones [50], flavonoids, stigmaasterol, 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 practices and 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 ethnomedical, 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 mechanism

1. Inhibition of lipid peroxidation as exhibited by *Garcinia mangostana* [54], *Alstonia scholaris* [55, 56] and *Annona muricata* [49, 57, 58].

2. Scavenging reactive oxygen species (ROS) as shown by *Abras agglutinin* and *Allium sativum* [59, 60] and normalizes in (APF) levels in *Allium sativum* [33].

3. Inhibiting proliferation via the activation of caspase-3 and caspase-9, up-regulation of the ratio of BD/bcl-2 protein expression in *Ardisia brevicaulis* [61], *Artocarpus obtusus* [50, 62], *Ardisia brevicaulis* [63], *Carica papaya* [64], *Catharanthus roseus* [118-119], *Costus speciosus* [121-122], *Cucumis melo* [65], *Dysosyrum ciliatum* [66], *Goniostolahus macrophyllus* [137-138], *Gymnura procumbens* [139], *Lawsonia inermis* [56, 146-147], *Leuca indica* [148-149], *Nepthelium lappaceum* [56, 156], *Pandanus amaryllifolius* [61], *Phyllanthus niruri* [67], *Physalis minima* [52, 78], *Rhodiol rosea* [68], *Vernonia amygdalina* [65] and *Schima wallichi* [68].

4. Induced mitochondrial and nuclear DNA damage like in *Curcuma 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 ant body synthesis and nearly inhibited the classical complement pathway like in *Boswellia serrata* [69, 70].

8. Cell morphological changes such as cyttoplasmic shrinkage, condensation of nucleus and formation of membrane-bound vesicles in *Abras precatorius* [59, 71] and *Scurrula ferruginea* [88, 166].

9. Expression levels of apoptosis-related genes (caspase-3 and caspase-9) *Tinospora crispa* [72], *Andrographis paniculata* [67, 101-102], *Brassica oleracea* [63, 80, 111], *Curcuma xanthorrhiza* [73], *Euphorbia cotinum* [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 *Dillenia suffruticosus* [74] also in *Z. officinalis* [48], *Juglans regia* [47], *L. pumilla* [75] and *T. foenum* [76] and on the other hand, the use of pro-apoptotic genes like caspases, 3, 7, 8 and 9, and PS3 have made 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* [90], *Anisochilus carnosus*, *P. minima* [52,96], *Sandoricum koetjape* [89], *E. cotonii* [43], *C. xanthorrhiza* [40], *Nigella sativa* [99], *R. rosae* [94], *Sanchezia speciosa* [100], and *Ipomoea quamoclit* [101], and those with least apoptosis were *Phylla nodiflora* [102], *Brassica oleracea* [97], *Murraya koenigii* [42], and *Hyphophyton formicarum* [103] while those plant that shows apoptosis with morphological changes includes *E. longifolia* [85], *S. ferruginea* [104], *Syzygium aromaticum* [63], *C. longa* [33,77], *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. conchiígara* [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 ethnomedical, 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⁺ homoeostasis, 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 millenial 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 practitioners 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, Fahlaceae, Loranthaceae, Malvaaceae, Moraceae, Amaryllidaceae, Araceae, Solanaceae, Acanthaceae, Apocynaceae, Liliaceae, Rubiaceae, Apliacae, Lauraceae, and Pipervaceae (in order of appearance) which have diverse uses in traditional medicine, some of the phytochemicals with potency includes Anonaine, Atisine, genistein, glistein, ritun, pymaein, antfincein, aspreuloside, calotoxin, caltopxin, bauhinioxin, bauhiniatatins, caratol, and xanthorrhizin, 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 the treatment of breast cancer.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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