

MALAYSIAN MEDICINAL PLANTS' POTENTIAL FOR BREAST CANCER THERAPY

MUHAMMAD MURTALA MAINASARA^{1,2}, MOHD FADZELLY ABU BAKAR^{1*}, ALONA C LINATOC¹

¹Department of Technology and Natural Resources, Faculty of Applied Sciences and Technology, Universiti Tun Hussein Onn Malaysia, Hub Pendidikan Tinggi Pagoh, KM1, Jalan Panchor, 84600, Muar, Johor, Malaysia. ²Department of Biological Sciences, Usmanu Danfodiyo University Sokoto (UDUS) PMB 1026 Sokoto State Nigeria. Email: fadzelly@uthm.edu.my

Received: 20 December 2017, Revised and Accepted: 19 March 2018

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 (IC₅₀ 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.

© 2018 The Authors. Published by Innovare Academic Sciences Pvt Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>) DOI: <http://dx.doi.org/10.22159/ajpcr.2018.v11i6.24322>

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, interleukin2, 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 $\mu\text{g}/\text{mL}$, *Bauhinia purpurea* with IC_{50} value of 9 $\mu\text{g}/\text{mL}$ for MCF-7 and IC_{50} value of 17 $\mu\text{g}/\text{mL}$ for MDA-231, *Calotropis gigantea* with IC_{50} value of 1.3 $\mu\text{g}/\text{mL}$ for MCF-7 and IC_{50} value of 3.3 $\mu\text{g}/\text{mL}$ for MDA-231, *Piper nigrum* with IC_{50} value of 13 $\mu\text{g}/\text{mL}$, *Casearia capitellata* with IC_{50} value of 2 $\mu\text{g}/\text{mL}$ 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
<i>Abrus precatorius</i> /jequirity	Fabaceae	Saga	Lectin	MDA-MB-231L. (in vitro)	Significant morphological changes such as shrinking of cytoplasm, condensation of nucleus, and formation of membrane-bound vesicles	[39,59,84]
<i>Albizia zygia</i> /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]
<i>Allium cepa</i> (Onion)	Liliaceae	Bawang putih	Diallyl trisulfide	MCF-7 (in vitro)	Increase histone acetylation	[30]
<i>Allium sativum</i> /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]
<i>Alpinia conchigera</i>	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]
<i>Alpinia officinarum</i> /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]
<i>Alternanthera tenella</i>	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]
<i>Alstonia scholaris</i> /blackboard/scholar tree	Apocynaceae	Pulailimin	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]
<i>Amaranthus lividus</i> /slender amaranth	Amaranthaceae	Bayamhijau	β-carotene and amygdalin	MCF7 and MDA-MB-231 (in vitro)	Inhibiting peroxidation of phosphatidylcholine liposomes persuaded with Fe ³⁺ /ascorbate to scavenge ABTS, DPPH and hydroxyl radicals, to lessen Fe (III) to Fe (II) and to chelate Fe (II)	[58,87]
<i>Amaranthus gangeticus</i> /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]
<i>Andrographis paniculata</i> /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]
<i>Ardisia crispa</i> /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
<i>Annona muricata</i> /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) Anti-proliferation activity with IC ₅₀ value of 10ug/ml, of MCF-7 by apoptosis induction	[49,57]
<i>Annona squamosa</i> /sugar apple	Annonaceae	Buahnona	Atisine, oxophoebine, and reticuline	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]
<i>Ardisia brevicaulis</i> /coralberry or marlberry	Myrsinaceae	Mabberi	Ardisiacrispins A and B	MCF-7 (in vitro)	Decreases histone methylation (H3K4 and H3R17); HMTi (G9a), in vitro HATi and decreases histone acetylation	[30]
<i>Argemone mexicana</i> /Mexican poppy	Papaveraceae		Sanguinarine and dihydrosanguinarine	MCF-7 (in vitro)	Exhibiting strong free radical scavenger towards DPPH with IC ₅₀ value of 2 µg/mL with prominent discoloration	[121,122]
<i>Artocarpus altilis</i> /breadfruit	Moraceae	Sukun	Pyranocycloartobioxanthone A, and B dihydro-artoindonesiamin C,	MCF-7 (in vitro)	Caspase-3 and caspase-9 enzymes activation and upregulation of the ratio of Bax/bcl-2 protein expression	[50]
<i>Artocarpus obtusus</i> /breadfruit	Moraceae	Lempoyang	Pyranocycloartobito xanthone A	MCF7 (in vitro)	Organelle organization alteration, cellular plan, and differentiation degree, cellular metabolism	[69]
<i>Azadirachta indica</i> /neem tree	Meliaceae	Mambu	Azadirachtin, limonoid	MDA-MB 231 (in vitro)	Active against MCF-7 at (IC ₅₀ ≈ 9 µg/mL), and MDA-MB 231 at IC ₅₀ ≈ 17 µg/mL)	[123,90]
<i>Bauhinia purpurea</i> /butterfly tree	Fabaceae	Tapakkuda	Bauhiniaastatins, lutein, and B-sitosterolbauhinoxepin	MCF-7 and MDA-MB 231 (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]
<i>Brassica oleracea</i> /cabbage	Brassicaceae	Kubis	β-carotene, lutein, α-Tocopherol	MCF-7 (in vitro)	Declined in polymorphonuclear leukocyte infiltration and migration, reduced primary antibody synthesis and nearly inhibited the classical complement pathway	[82,83]
<i>Boswellia serrata</i> /Indian olibanum	Burseraceae	Nhau	Boswellic acid	MCF-7 (in vitro)	DTN treatment significantly arrested MCF-7 cells at the G0/G1 phase (po0.05), and ROS was significantly elevated. Moreover, DTN significantly blocked the induced translocation of NF-kB from the cytoplasm to the nucleus	[125]
<i>Clausena excavata</i>	Rutaceae	Daunsicerek, cherekhitam	Dentatin	MCF-7 (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]
<i>Calotropis gigantea</i> /crown flower	Apocynaceae	Remiga, kemengu	Calotropin, frugoside, calotoxin	MCF-7 and MDA-MB-231 (in vitro)	Hindering production in LPS-stimulated RAW 264.7 macrophages	[127,128]
<i>Capsicum annuum</i> /red chilli	Solanaceae	Cili	Capsaicin, myricetin; a bioflavonoid	MCF-7 (in vitro)		

(Contd...)

Table 1: (Continued)

Plant name/common name	Family	Local name (Malay)	Active compound	Experimental model	Mechanism of action	Source
<i>Carica papaya/pawpaw</i>	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]
<i>Casearia capitata</i>	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]
<i>Catharanthus roseus</i>	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]
<i>Centratherum anthelminticum/black cumin</i>	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	[105]
<i>Coriandrum sativum</i>	Apiaceae	Ketumbar	apinene, limpnene, 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	[67]
<i>Curcuma longa/Turmeric</i>	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 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	[30,33,37]
<i>Coriandrum sativum/coriander</i>	Apiaceae	Ketumbar	Flavonoids	MCF-7 (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	[95]
<i>Cheilocostus speciosus/crêpe ginger</i>	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]
<i>Cymbopogon citratus/lemon grass</i>	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]
<i>Curcuma amada/mango ginger</i>	Zingiberaceae	Manjellakua	Curcuminoids	MDA-MB-231 and MCF-7 (in vitro)	Expression of hTERT mRNAs and not hTER were inhibited	[39]
<i>Curcuma xanthorrhiza/false turmeric</i>	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]
<i>Curcuma zedoaria</i>	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
<i>Dendrophthoe falcata</i> /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]
<i>Dendrophthoe pentandra</i> /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]
<i>Dillenia suffruticosa</i>	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]
<i>Dysoxylum cauliflorum</i>	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]
<i>Echinacea angustifolia</i> /coneflower <i>Etingera elatior</i> /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]
<i>Eucheuma cottonii</i> /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]
<i>Eurycoma longifolia</i> /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	[85,140]
<i>Elephantopus scaber</i> /elephant's foot	Asteraceae	Tutup bumi	Deoxyelephantopin	MCF-7 (in vitro)	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)	[141]
<i>Eupatorium odoratum</i> /Siam weed	Asteraceae	Rumpat Pahang, rumpupait	Triterpenoids, flavonoids	MDA-MB-231 (in vitro)	Inhibiting growth and triggered time-dependent and dosage-dependent cell death in the MCF-7 via p53 dependent apoptotic pathway	[142]
<i>Ficus deltoidea</i> /mistletoe fig	Moraceae	Mas cotek	Moretenol, quercetin-3-rutinoside	MCF-7	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	[71]
<i>Garcinia mangostana</i> /Mangosteen	Clusiaceae	Manggis, mangusta	Mangostin	3T3 and 4T1 cells (in vitro)	Inhibited cell proliferation Lipid peroxidation inhibition	[56]

(Contd...)

Table 1: (Continued)

Plant name/common name	Family	Local name (Malay)	Active compound	Experimental model	Mechanism of action	Source
<i>Goniothalamus macrophyllus</i> /airy shaw	Thymelaeaceae	Selada, selayar hitam	Styrylpyrone, goniothalamine-β-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]
<i>Glycine max</i> , (soybean)	Fabaceae	Bean	Genistein and Daidzein	MCF-7 (in vitro)	Gene reactivation (p16, RARbeta, and MGMT), induces DNA demethylation	[30]
<i>Gynura procumbens</i> /longevity spinach	Steraceae	Dewa raja, Akarsebiak, Kachamakkar.	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]
<i>Hedyotis corymbosa</i> /diamond-flower	Rubiaceae	Siku-siku, LidahUlar, Rumpuit Mutiara Getah	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]
<i>Hevea brasiliensis</i> /rubber tree	Euphorbiaceae	Simbag hutak	Latex B-serum	MCF-7 (in vitro)	Regulate intrinsic and extrinsic apoptotic pathways in MCF-7	[103]
<i>Hydnophytum formicarum</i> /Caudex	Rubiaceae		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]
<i>Hyptis suaveolens</i>	Lamiaceae	Lerkuang 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]
<i>Ipomoea quamoclit</i> /morning-glory	Convolvulaceae	Kangkung	Flavonoids	MCF-7 and 3T3 cell line (in vitro)	Inhibit the proliferation, migration, and invasion of pro-metastatic and scycloxygenase-2 (COX-2). Ipobscurine may also promote apoptosis by up-regulating pro- and also suppresses various TF, arrest at G1	[101]
<i>Juglans regia</i> /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]
<i>Labisia pumila</i> /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]
<i>Lawsonia inermis</i>	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]

(Contd...)

Table 1: (Continued)

Plant name/common name	Family	Local name (Malay)	Active compound	Experimental model	Mechanism of action	Source
<i>Leea indica</i> /Bandicoot berry	Vitaceae	Mali-mali, merbatipadang, jolok-jolok Pengolaban	Palmitic acid, 1-eicosanol, solanesol	MCF-7 and T47D	Inhibition of proliferation	[77,148]
<i>Litsea garciae</i> /Engkala	Lauraceae		Alkaloid, flavonoids, chalcone	MCF-7 (in vitro)	Cytotoxicity activity was exhibited moderately with IC ₅₀ value of 73 µg/ml against MCF-7	[149]
<i>Mangifera indica</i> /Mango	Anacardiaceae	Mangga	Vimang, mangiferin	MCF-7 and MDA-MB-231 cell lines	Inhibiting NFIB target genes that are involved in inflammation, anti-apoptosis metastasis, and angiogenesis	[44,150]
<i>Muntingia calabura</i> /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]
<i>Mangifera pajang</i>	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]
<i>Melastoma malabathricum</i>	Melastomataceae	SendudukPutih	Malvidin-3,5-diglucoside	(MCF-7) in vitro	Inactivation of tumour suppressor genes such as p53	[151]
<i>Morinda citrifolia</i> /Cheese fruit	Rubiaceae	Mengkudu	Damnacanthal,	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]
<i>Moringa oleifera</i> /Drumstick	Moringaceae	Kacangkelo	Isoquercetin and astragalgin	MCF-7 in vitro	Inhibited MCF-7 cell line with 87.13% in average at wavelength A570 nm	[45,152]
<i>Murraya koenigii</i> /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]
<i>Murraya paniculata</i> /Orange Jessamine	Rutaceae	Kemuning	(E)-caryophyllene	MCF-7 (in vitro)	Cytotoxicity activity against MCF-7	[78]
<i>Nephelium lappaceum</i> /Rambutan	Sapindaceae	Rambutan	Trypsin and α-chymotrypsin, dithiothreitol	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]
<i>Nigella sativa</i> /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]
<i>Orthosiphon stamineus</i> /"cat whisker"	Lamiaceae	Java tea/ misaikuicing	Rosmarinic acid	MCF-7 (in vitro)	Enhancing anti-proliferative activity of TMX against MCF-7	[155]
<i>Pandanus amaryfolius</i> /Pandanus 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]

(Contd...)

Table 1: (Continued)

Plant name/common name	Family	Local name (Malay)	Active compound	Experimental model	Mechanism of action	Source
<i>Persea declinata</i>	Lauraceae	Medanginai	α -humulene	MCF-7 (<i>in vitro</i>)	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 inhibitory concentration (IC ₅₀) of 10.4±0.06 µg/mL	[80]
<i>Peperomia pellucida</i> /Pepper elder	Piperaceae	Ketumpang air	Carotol, dill apiole, pygmaein	(MCF-7) cell line (<i>in vitro</i>)	Cytotoxic activity against MCF-7 with IC ₅₀ between 25.5 and 40.8 µg/mL	[156,157]
<i>Phaleria macrocarpa</i> /Crown of God	Thymelaeaceae	Mahkotadewa	Rutin, ferric thiocyanate and thiobarbituric acid	MCF-7 (<i>in vitro</i>)	Exhibited cytotoxic activity, h IC ₅₀ values ranging 7.5–13.4 µg/mL (17.1–30.5 µM)	[158]
<i>Phyllanthus pulcher</i> /Weed	Phyllanthaceae	Keluruttanjong, nagabuana	Triterpenoids (lupane)	MCF-7 (<i>in vitro</i>)	Anti-proliferation and Apoptotic DNA fragmentation of MCF7 were inhibited by all the extracts with IC ₅₀ ranging from 90 to 120 µg/mL	[65]
<i>Phyla nodiflora</i> /matchweed	Verbenaceae	Pact-pac	Nodifloretin, larycitrin, β -sitosterol	MCF-7 (<i>in vitro</i>)	Anti-proliferation of NCI-H23 by proposed to be facilitated by caspase-3, p53 and c-myc-dependent apoptosis pathways	[100]
<i>Physalis minima</i> /bladder cherry	Solanaceae	Letup-letup, rumpuemeranti	Withanone A, stigmastanol and withaferin A	MCF 7 <i>in vitro</i>	Cytotoxic with an IC ₅₀ value of 13.0 µg/mL	[52,96]
<i>Piper nigrum</i> /black pepper	Piperaceae	Lada Hitam	Pellitorine	MCT-7 cell lines (<i>in vitro</i>)	Increased in catalase activities and superoxide dismutase in the treated cells may alter the antioxidant defence system	[159]
<i>Piper betle</i> /betel	Piperaceae	Sirih, suruh, seureuh	Catechin, morin, and quercetin	HL60 and MCF-7 cell lines	Anti-proliferative activity in MDA-showed the cytotoxicity of IC ₅₀ of 4.23 µg/mL	[159]
<i>Psidium guajava</i> /guava	Myrtaceae	Jambu Batu	Catechin, Rutin and Quercetin	MDA-MB-231 (<i>in vitro</i>)	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 SDF1 α	[117,160]
<i>Punica granatum</i> /pomegranate	Lythraceae	Pokok Delima	Ellagitannins	MDA-MB-231 and MCF-7 (<i>in vitro</i>)		[161]
<i>Pueraria mirifica</i>	Fabaceae		Daidzein	MCF-7 (<i>in vitro</i>)	Gene reactivation (p16, RARbeta, and MGMT), induces DNA demethylation	[30]
<i>Pueraria lobata</i> (Willdenow)	Fabaceae		Daidzein	MCF-7 (<i>in vitro</i>)	Gene reactivation (p16, RARbeta, and MGMT), induces NA demethylation	[30]
<i>Raphanus sativus</i> /white radish	Brassicaceae	Putih	Raphasativuside A B, phenylpropanoidsucrosides 1–7	MDA-MB-231 and MCF-7 (<i>in vitro</i>)	Cytotoxicity against all the tested cell lines, with IC ₅₀ values from 6.71–27.92 IM.	[162]
<i>Rhodiola rosea</i> /golden root, rose root	Crassulaceae		Rhodioloside and salidroside	MDA-MB-231 and MCF-7 (<i>in vitro</i>)	Antiproliferation and inducing apoptotic cell death in ER-negative and ER-positive MCF-7 and MDA-MB-231	[94,86]

(Contd...)

Table 1: (Continued)

Plant name/common name	Family	Local name (Malay)	Active compound	Experimental model	Mechanism of action	Source
<i>Sandoricum koetjape</i> (Santol or cottonfruit)	Meliaceae.	Sentiel, 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]
<i>Sanguinaria Canadensis</i> (blood root)	Papaveraceae		Sanguinarine	MCF-7 (in vitro)	Decreases histone methylation (H3K4 and H3R17); HMT1 (G9a), in vitro HAT1 and decreases histone acetylation	[30]
<i>Scurrula ferruginea</i> /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]
<i>Silybum marianum</i> (milk thistle)	Asteraceae		Silibinin	MCF-7 (in vitro)	Increases histone acetylation	[30]
<i>Syzygium aromaticum</i> /Cloves	Myrtaceae	Bungacingkeh	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]
<i>Sanchezia speciosa</i> /Shrubby white vein	Acanthaceae		Quercetin	MCF-7 (in vitro)	Inhibition activity on HUVEC cells	[100]
<i>Schima wallichii</i> /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]
<i>Strobilanthes crispus</i> /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]
<i>Tinospora crispa</i> /Heart-leaved, Batawali	Menispermaceae	Batawali or seruntun or AlkarPutarwali	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]
<i>Trigonella foenum</i> /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]
<i>Vernonia amygdalina</i> /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]
<i>Thelesperma megapotamicum</i> /Pampa tea	Asteraceae	Tetiup	Luteolin, and phenylpropanoids	MCF-7 (in vitro)	Inhibition in cultured MCF-7 cells	[167,168]
<i>Theobroma cacao</i> /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]
<i>Typhonium flagelliforme</i> \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]

(Contd...)

Table 1: (Continued)

Plant name/common name	Family	Local name (Malay)	Active compound	Experimental model	Mechanism of action	Source
<i>Vaticadlos pyroides</i> /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]
<i>Withania somnifera</i> /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]
<i>Zingiber officinale</i> /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

corymbosa with IC₅₀ value of 6.51 μ g/mL in MCF-7 and IC₅₀ value of 2.75 μ g/mL in MDA-231, *Nepheium lappaceum* with 100% inhibition at IC₅₀ value of 8 μ g/mL, *Psidium guajava* in MDA showed the cytotoxicity of IC₅₀ of 4.23 μ g/mL, *Peperomia pellucida* with IC₅₀ value of 10.4 μ g/mL, *Phaleria macrocarpa* with IC₅₀ value of 25.5–40.8 μ g/mL, *Curcuma xanthorrhiza* IC₅₀ value of 1.71 \pm 0.1 μ g/mL, *Mangifera pajang* with IC₅₀ value of 23 μ g/mL in MCF-7 and IC₅₀ value of 30.5 μ g/mL in MDA-231 and *Phyllanthus pulcher* with IC₅₀ value of 18.9 \pm 0.7 μ g/mL while most of the lowest activities were found in *Etingera elatior* with IC₅₀ value of 173.1 μ g/mL in MCF-7 and IC₅₀ value of 196.2 μ g/mL in MDA-231, *Albizia zygia* with IC₅₀ value of 83.16 μ g/mL, *Litsea garciae* with IC₅₀ value of 73 μ g/mL, *Phyla nodiflora* with IC₅₀ value of 90–120 μ g/mL, *Moringa oleifera* with IC₅₀ value of 87.13 μ g/mL, *Artocarpus altilis* exhibiting strong free radical scavenger towards DPPH with IC₅₀ value of 2 μ g/mL, and *Amaranthus gangeticus* with IC₅₀ value of 98.8 μ g/mL, *Dendrophthoe pentandra* with IC₅₀ value of 107 μ g/mL in MCF-7 and IC₅₀ value of 112 μ g/mL in MDA-231, and *Trigonella foenum* and *Theobroma cacao* with IC₅₀ value of 41.4 μ g/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 pyranocycloartobioxanthone A (PA), dihydro-artoindonesianin C, and pyranocycloartobioxanthone B isolated from *Artocarpus obtusus* and shows strong cytotoxic activity against MCF-7 and MDA-MB-231 with IC50 values of 5.0 μ g/mL in) at 30 μ g/mL concentration and IC50 value of 2 μ g/ in *Artocarpus altilis*. Dentatin also isolated from *Clausena 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 IC₅₀ 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. Damacanthol 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 *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 IC₅₀ value of 24.85 μ g/ml. 1'S-1'-Acetoxychavicol acetate (ACA) isolated from *Alpinia conchigera* induced cell cycle arrest at G0/G1 phase with IC₅₀ values 34.0 μ M to 48.0 μ M. Xanthorrhizol isolated from the rhizome of *Curcuma xanthorrhiza* inhibites proliferation of MCF-7 with an EC₅₀ value of 1.71 μ g/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 IC₅₀ of 0.53 \pm 0.19 μ g/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 IC₅₀ 15.23 \pm 0.66 μ g/ml in MCF-7 but is less sensitive against MCF-10A with IC₅₀ 66.31 \pm 0.47 μ g/

ml. Alkenylresorcinols, labisiaquinone A and labisiaquinone 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, nodifloretin, β silosterol, mangiferonic acid, pellitorine, kaempferol [38], curcumin, curcuminoids, α-turmerone, [33,37,39,40], quercetin [41,42], catechin, rutin [43], xanthorrhizol [40], mangiferin [44], ferric thiocyanate, thiobarbituric acid, isoquercetin, astragalins [45], damnacanthol [46], naphthoquinones [47], triterpenoids, flavonoids, gallic acid, gingerol [48] anonaine, isolauriline, annonamine [49], xanthonols [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 cauliflorum* [66], *Goniosthalamus macrophyllus* [137-138], *Gynura procumbens* [139], *Lawsonia inermis* [56,146-147], *Leea indica* [148-149], *Nepthelium lappaceum* [56,156] *Pandanus amaryfolius* [41], *Phyla nodiflora* [67], *Physalis minima* [52, 78], *Rhodiola rosea* [68], *Vernonia amygdalina* [65] and *Schima wallichii* [38].
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 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 paniculata* [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-apoptotic genes like caspases, 3, 7, 8

and 9, and P53 has make a clear expression 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 oleracea* [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, pymaain, 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.

ACKNOWLEDGMENT

This research was supported by University Tun Hussein Onn Malaysia (UTHM) for providing internal research funding (GPPS, Vot: U608).

COMPETING INTERESTS

The authors declare that they have no competing interests.

REFERENCES

- Sawadogo WR, Schumacher M, Teiten MH, Dicato M, Diederich M. Traditional west african pharmacopeia, plants and DERIVED compounds for cancer therapy. *Biochem Pharmacol* 2012;84:1225-40.
- Dawson SJ, Makretsov N, Blows FM, Driver KE, Provenzano E, Le Quesne J, et al. BCL2 in breast cancer: A favourable prognostic marker across molecular subtypes and independent of adjuvant therapy received. *Br J Cancer* 2010;103:668-75.
- Amin A, Mousa M. Merits of anti-cancer plants from the Arabian Gulf region. *Cancer Ther* 2007;5:55-66.
- Kurman RJ. Cancer IAFRo, Organization WH: WHO Classification of Tumours of Female Reproductive Organs: International Agency for Research on Cancer; 2014.
- Abu Bakar MF, Abdul Karim F, Suleiman M, Isha A, Rahmat A. Phytochemical constituents, antioxidant and antiproliferative properties of a liverwort, *lepidozia borneensis stephani* from mount kinabalu, sabah, malaysia. *Evid Based Complement Alternat Med* 2015;2015:936215.
- Mohanlal S. Phytochemical Investigations on 'Black Glumed'njavara (*Oryza sativa* L.), the Medicinal Rice, as Compared to Staple Varieties and Evaluation of their Antioxidant, Anti-inflammatory and Anticancer Effects. Pennsylvania State University: Citeseer; 2011.
- Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin* 2015;65:5-29.
- Hussein R, Anuar H. Report of the Second National Health and Morbidity Survey Conference. Hospital Kuala Lumpur; 1997. p. 22.
- Norsa'adah B, Rusli BN, Imran AK, Naing I, Winn T. Risk factors of breast cancer in women in kelantan, malaysia. *Singapore Med J* 2005;46:698-705.
- Khazir J, Mir BA, Pilcher L, Riley DL. Role of plants in anticancer drug discovery. *Phytochem Lett* 2014;7:173-81.
- Bhoo-Pathy N, Yip CH, Hartman M, Uiterwaal CS, Devi BC, Peeters PH, et al. Breast cancer research in asia: Adopt or adapt western knowledge? *Eur J Cancer* 2013;49:703-9.
- Lim GC. Overview of cancer in Malaysia. *Jpn J Clin Oncol* 2002;32Suppl 1:S37-S42.
- von Minckwitz G, Untch M, Blohmer JU, Costa SD, Eidtmann H, Fasching PA, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. *J Clin Oncol* 2012;30:1796-804.
- Cazzaniga M, Bonanni B. Breast cancer chemoprevention: Old and new approaches. *BioMed Res Int* 2012;2012:985620.
- Sinha D, Biswas J, Sung B, Aggarwal BB, Bishayee A. Chemopreventive and chemotherapeutic potential of curcumin in breast cancer. *Curr Drug Targets* 2012;13:1799-819.
- Davies C, Pan H, Godwin J, Gray R, Arriagada R, Raina V, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at five years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet* 2013;381:805-16.
- Waters EA, McNeel TS, Stevens WM, Freedman AN. Use of tamoxifen and raloxifene for breast cancer chemoprevention in 2010. *Breast Cancer Res Treat* 2012;134:875-80.
- Chumsri S, Howes T, Bao T, Sabnis G, Brodie A. Aromatase, aromatase inhibitors, and breast cancer. *J Steroid Biochem Mol Biol* 2011;125:13-22.
- Tutt A, Robson M, Garber JE, Domchek SM, Audeh MW, Weitzel JN, et al. Oral poly (ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: A proof-of-concept trial. *Lancet* 2010;376:235-44.
- Gianni L, Dafni U, Gelber RD, Azambuja E, Muehlbauer S, Goldhirsch A, et al. Treatment with trastuzumab for 1 year after adjuvant chemotherapy in patients with HER2-positive early breast cancer: A 4-year follow-up of a randomised controlled trial. *Lancet Oncol* 2011;12:236-44.
- Rebucci M, Michiels C. Molecular aspects of cancer cell resistance to chemotherapy. *Biochem Pharmacol* 2013;85:1219-26.
- Holohan C, Van Schaeybroeck S, Longley DB, Johnston PG. Cancer drug resistance: An evolving paradigm. *Nat Rev Cancer* 2013;13:714-26.
- Safarzadeh E, Sandoghchian Shotorbani S, Baradaran B. Herbal medicine as inducers of apoptosis in cancer treatment. *Adv Pharm Bull* 2014;4:421-7.
- Aliya S, Devi YP, Uma A. Plants as potential resources of anticancer drugs. *Curr Trends Biotechnol Pharm* 2016;10:92-107.
- Nagaprashanthi CH, Kannan M, Karthikeyan M, Aleemuddin MA. Ethnomedicinal plants for prevention and treatment of breast cancer: A review. *Int J Pharm Sci Res* 2012;3:756.
- Omogbadegun ZO. Medicinal plants-based foods for breast cancer treatment: An ethnobotanical survey and digitization. *Int J Med Plants Alt Med* 2013;1:137-63.
- Sa L. Top 3 herbal drugs for breast cancer. *Int J PharmTech Res* 2013;5:1811-5.
- Islam M, Aksharin L, Ahmed A, Moududee SA, Hossain M, Rahman M, et al. Herbal medicinal plant in the treatment of breast cancer-an overview. *Int J Pharm Life Sci* 2014;5:575-82.
- Levitsky DO, Dembitsky VM. Anti-breast cancer agents derived from plants. *Nat Prod Bioprospect* 2014;5(1):1-16.
- Elgadir MA, Salama M, Adam A. Anti-breast cancer from various natural sources-review. *Int J Pharm Pharm Sci* 2015;4:1142-53.
- Jaikumar B, Jasmine R: A Review on a few medicinal plants possessing anticancer activity against human breast cancer. *Int J PharmTech Res* 2016;9:333-65.
- Shareef M, Ashraf MA, Sarfraz M. Natural Cures for Breast Cancer Treatment. *Mini Rev Med Chem* 2016;16:596-604.
- Nataru S, Pulicherla Y, Gaddala B. A review on medicinal plants as a potential source for cancer. *Int J Pharm Sci Res* 2014;26:235-48.
- Jordan VC. Molecular mechanisms of antiestrogen action in breast cancer. *Breast Cancer Res Treat* 1994;31:41-52.
- Seery L, Gee J, Dewhurst O, Nicholson RI. Molecular mechanisms of antiestrogen action. In: *Estrogens and Antiestrogens*. 1st ed. New York: Springer; 1999. p. 201-20.
- Osborne CK, Schiff R. Mechanisms of endocrine resistance in breast cancer. *Annu Rev Med* 2011;62:233-47.
- Yue GG, Chan BC, Hon PM, Lee MY, Fung KP, Leung PC, et al. Evaluation of *in vitro* anti-proliferative and immunomodulatory activities of compounds isolated from *Curcuma longa*. *Food Chem Toxicol* 2010;48:2011-20.
- Diantini A, Subarnas A, Lestari K, Halimah E, Susilawati Y, Supriyatna, et al. Kaempferol-3-O-rhamnoside isolated from the leaves of *schima wallichii* korth. Inhibits MCF-7 breast cancer cell

- proliferation through activation of the caspase cascade pathway. *Oncol Lett* 2012;3:1069-72.
39. Manoharan S, Kaur J. Anticancer, antiviral, antidiabetic, antifungal and phytochemical constituents of medicinal plants. *Am J PharmTech Res* 2013;3:149-69.
 40. Cheah YH, Azimahtol HL, Abdullah NR. Xanthorrhizol exhibits antiproliferative activity on MCF-7 breast cancer cells via apoptosis induction. *Anticancer Res* 2006;26:4527-34.
 41. Zan CH, Rahmat A, Abdah MDA, Akim M, Alitheen NB, Othman F, et al. Anti-proliferative effects of pandan leaves (*Pandanus amaryfolius*), kantan flower (*Etilingera elatior*) and turmeric leaves (*Curcuma longa*). *Nutr Food Sci* 2011;41:238-41.
 42. Ghasemzadeh A, Jaafar HZ, Rahmat A, Ashkani S. Secondary metabolites constituents and antioxidant, anticancer and antibacterial activities of *Etilingera elatior* (Jack) RM Sm grown in different locations of Malaysia. *BMC Complement Altern Med* 2015;15:1.
 43. Namvar F, Mohamed S, Fard SG, Behravan J, Mustapha NM, Alitheen NB, et al. Polyphenol-rich seaweed (*Euclidean cottonii*) extract suppresses breast tumour via hormone modulation and apoptosis induction. *Food Chem* 2012;130:376-82.
 44. Abdullah AS, Mohammed AS, Abdullah R, Mirghani ME, Al-Qubaisi M. Cytotoxic effects of *Mangifera indica* L. Kernel extract on human breast cancer (MCF-7 and MDA-MB-231 cell lines) and bioactive constituents in the crude extract. *BMC Complement Altern Med* 2014;14:199.
 45. Hossain N, Mirghani M, Raus RB. Optimization of *Moringa oleifera* leaf extraction and investigation of anti breast cancer activity with the leaf extract. *Eng Int* 2015;3:97-103.
 46. Aziz MY, Omar AR, Subramani T, Yeap SK, Ho WY, Ismail NH, et al. Damnacanthal is a potent inducer of apoptosis with anticancer activity by stimulating p53 and p21 genes in MCF-7 breast cancer cells. *Oncol Lett* 2014;7:1479-84.
 47. Hasan TN, B LG, Shafi G, Al-Hazzani AA, Alshatwi AA. Anti-proliferative effects of organic extracts from root bark of *Juglans regia* L. (RBJR) on MDA-MB-231 human breast cancer cells: Role of bcl-2/Bax, caspases and tp53. *Asian Pac J Cancer Prev* 2011;12:525-30.
 48. Rahman S, Salehin F, Iqbal A. *In vitro* antioxidant and anticancer activity of young *Zingiber officinale* against human breast carcinoma cell lines. *BMC complement Altern Med* 2011;11:1.
 49. Endrini S, Suherman S, Widowati W. *Annona muricata* leaves have strongest cytotoxic activity against breast cancer cells. *Univ Med* 2015;33:179-84.
 50. Hashim NM, Rahmani M, Ee GC, Sukari MA, Yahayu M, Oktima W, et al. Antiproliferative activity of xanthenes isolated from *Artocarpus obtusus*. *J Biomed Biotechnol* 2012;2012:130627.
 51. Sani HA, Rahmat A, Ismail M, Rosli R, Endrini S. Potential anticancer effect of red spinach (*Amaranthus gangeticus*) extract. *Asia Pac J Clin Nutr* 2004;13:396-400.
 52. Ooi KL, Tengku Muhammad TS, Lim CH, Sulaiman SF. Apoptotic effects of physalis minima L. Chloroform extract in human breast carcinoma T-47D cells mediated by c-myc-, p53-, and caspase-3-dependent pathways. *Integr Cancer Ther* 2010;9:73-83.
 53. Park SY, Kim HJ, Kim KR, Lee SK, Lee CK, Park KK, et al. Betulinic acid, a bioactive pentacyclic triterpenoid, inhibits skeletal-related events induced by breast cancer bone metastases and treatment. *Toxicol Appl Pharmacol* 2014;275:152-62.
 54. Jagetia GC, Baliga MS. Modulation of antineoplastic activity of cyclophosphamide by *Alstonia scholaris* in the ehrlich ascites carcinoma-bearing mice. *J Exp Ther Oncol* 2003;3:272-82.
 55. Jayanthi G, Smitha K. *In vitro* evaluation of the anticancer effect of methanolic extract of *Alstonia scholaris* leaves on mammary carcinoma. *J Appl Pharm Sci* 2012;2:142.
 56. Ling LT, Radhakrishnan AK, Subramaniam T, Cheng HM, Palanisamy UD. Assessment of antioxidant capacity and cytotoxicity of selected Malaysian plants. *Molecules* 2010;15:2139-51.
 57. Syed Najmuddin SU, Romli MF, Hamid M, Alitheen NB, Nik Abd Rahman NM. Anti-cancer effect of *Annona muricata* linn leaves crude extract (AMCE) on breast cancer cell line. *BMC Complement Altern Med* 2016;16:311.
 58. Lee HM, Moon A. Amygdalin regulates apoptosis and adhesion in hs578T triple-negative breast cancer cells. *Biomol Ther (Seoul)* 2016;24:62-6.
 59. Bhatia SK, Behera B, Das DN, Mukhopadhyay S, Sinha N, Panda PK, et al. *Abrus agglutinin* is a potent anti-proliferative and anti-angiogenic agent in human breast cancer. *Int J Cancer* 2016;139:457-66.
 60. Capasso A. Antioxidant action and therapeutic efficacy of *Allium sativum* L. *Molecules* 2013;18:690-700.
 61. Chen LP, Zhao F, Wang Y, Zhao LL, Li QP, Liu HW, et al. Antitumor effect of resorcinol derivatives from the roots of *ardisia brevicaulis* by inducing apoptosis. *J Asian Nat Prod Res* 2011;13:734-43.
 62. Aisha AF, Abu-Salah KM, Alrokayan SA, Siddiqui MJ, Ismail Z, Majid AM. *Syzygium aromaticum* extracts as good source of betulinic acid and potential anti-breast cancer. *Rev Bras Farmacog* 2012;22:335-43.
 63. Devi JR, Thangam EB. Mechanisms of anticancer activity of sulforaphane from *Brassica oleracea* in HEP-2 human epithelial carcinoma cell line. *Asian Pac J Cancer Prev* 2012;13:2095-100.
 64. Arisanty D. *In vitro* cytotoxic study and detection of apoptosis on breast cancer cell lines MDA-MB 231 after exposed to *Azadirachta indica* A. juss (neem) extract. *J Kesehatan Andalas* 2013;2:80-4.
 65. Aslam J, Khan SH, Siddiqui ZH, Fatima Z, Maqsood M, Bhat MA, et al. *Catharanthus roseus* (L.) G. Don. An important drug: It's applications and production. *Pharm Glob (IJCP)* 2010;4:1-16.
 66. Ahmad NH, Rahim RA, Mat I. *Catharanthus roseus* aqueous extract is cytotoxic to Jurkat leukaemic T-cells but induces the proliferation of normal peripheral blood mononuclear cells. *Trop Life Sci Res* 2010;21:101.
 67. Rajalakshmi M, Anita R. *In vitro* and *in silico* evaluation of antioxidant activity of a sesquiterpene lactone, costunolide, isolated from *Costus speciosus* rhizome on mcf-7 and mda-mb-231 human breast cancer cell lines. *World J Pharm Pharm Sci* 2014;3:1334-47.
 68. El-Far AH, Badria FA, Shaheen HM. Possible anticancer mechanisms of some *Costus speciosus* active ingredients concerning drug discovery. *Curr Drug Discovery Technol* 2016;13:123-43.
 69. Andrade S. Physical, chemical and biochemical changes of sweetsop (*Annona squamosa* L.) and golden apple (*Spondias citherea* sonner) fruits during ripening. *J Agric Sci Technol B* 2012;2:1148.
 70. Bakar MF, Mohamed M, Rahmat A, Fry J. Phytochemicals and antioxidant activity of different parts of bambangan (*Mangifera pajang*) and tarap (*Artocarpus odoratissimus*). *Food Chem* 2009;113:479-83.
 71. Alabsi AM, Ali R, Ali AM, Harun H, Al-Dubai SA, Ganasegeran K, et al. Induction of caspase-9, biochemical assessment and morphological changes caused by apoptosis in cancer cells treated with goniothalamin extracted from *Goniothalamus macrophyllus*. *Asian Pac J Cancer Prev* 2013;14:6273-80.
 72. Seyed MA, Jantan I, Bukhari SN. Emerging anticancer potentials of *Goniothalamus* and its molecular mechanisms. *BioMed Res Int* 2014;2014:536508.
 73. Hew CS, Khoo BY, Gam LH. The anti-cancer property of proteins extracted from *Gynura procumbens* (Lour.) Merr. *PLoS One* 2013;8:e68524.
 74. Singh DK, Luqman S. *Lawsonia inermis* (L.): A perspective on anticancer potential of mehndi/henna. *Biomed Res Ther* 2014;1:112-20.
 75. El-Babili F, Bouajila J, Valentin A, Chatelain C. *Lawsonia inermis*: Its anatomy and its antimetabolic, antioxidant and human breast cancer cells MCF7 activities. *Pharm Anal Acta* 2013;4:1-6.
 76. Reddy NS, Navanesan S, Sinniah SK, Wahab NA, Sim KS. Phenolic content, antioxidant effect and cytotoxic activity of *Leea indica* leaves. *BMC Complement Altern Med* 2012;12:128.
 77. Nurhanan M, Asiah O, Ilham MM, Syarifah MS, Norhayati I, Sahira HL. Anti-proliferative activities of 32 Malaysian plant species in breast cancer cell lines. *J Trop For Sci* 2008;2008:77-81.
 78. Fang EF, Ng TB. A trypsin inhibitor from rambutan seeds with antitumor, anti-HIV-1 reverse transcriptase, and nitric oxide-inducing properties. *Appl Biochem Biotechnol* 2015;175:3828-39.
 79. Banerjee M, Chattopadhyay S, Choudhuri T, Bera R, Kumar S, Chakraborty B, et al. Cytotoxicity and cell cycle arrest induced by andrographolide lead to programmed cell death of MDA-MB-231 breast cancer cell line. *J Biomed Sci* 2016;23:40.
 80. Leong OK, Muhammad TS, Sulaiman SF. Cytotoxic activities of Physalis minima L. Chloroform extract on human lung adenocarcinoma NCI-H23 cell lines by induction of apoptosis. *Evid Based Complement Alternat Med* 2011;2011:185064.
 81. Suhail MM, Wu W, Cao A, Mondalek FG, Fung KM, Shih PT, et al. *Boswellia sacra* essential oil induces tumor cell-specific apoptosis and suppresses tumor aggressiveness in cultured human breast cancer cells. *BMC Complement Altern Med* 2011;11:129.
 82. Afsar V, Reddy M, Saritha K. *In vitro* antioxidant activity and anti-inflammatory activity of methanolic leaf extract of *Boswellia serrata*. *Int J Life Sci Biotech Pharm Res* 2012;1:15-23.

83. Sofi MS, Sateesh M, Bashir M, Harish G, Lakshmeesha T, Vedashree S, et al. Cytotoxic and pro-apoptotic effects of *Abrus precatorius* L. on human metastatic breast cancer cell line, MDA-MB-231. *Cytotechnology* 2013;65:407-17.
84. Ibahim M, Wan-Nor I, Narimah A, Sar SN, Froemming G. Anti-proliferative and antioxidant effects of *Tinospora crispa* (Batawali). *Biomed Res* 2011;22:57-62.
85. Marvibaigi M, Amini N, Supriyanto E, Abdul Majid FA, Kumar Jaganathan S, Jamil S, et al. Antioxidant activity and ROS-dependent apoptotic effect of *Scurrula ferruginea* (Jack) danser methanol extract in human breast cancer cell MDA-MB-231. *PLoS One* 2016;11:e0158942.
86. Marvibaigi M, Amini N, Supriyanto E, Jamil S, Majid FA, Khangholi S. Total phenolic content, antioxidant and antibacterial properties of *Scurrula ferruginea* extracts. *J Teknol* 2014;70:65-72.
87. Jadhao D, Thorat B. Purification (crystallization) of bioactive ingredient andrographolide from *Andrographis paniculata*. *World J Pharm Pharm Sci* 2014;3:747-63.
88. Hossain MS, Urbi Z, Sule A, Rahman K: *Andrographis paniculata* (Burm. f.) Wall. ex Nees: A review of ethnobotany, phytochemistry, and pharmacology. *Sci World J* 2014;2014:1-28.
89. Kuppusamy P, Ichwan SJ, Parine NR, Yusoff MM, Maniam GP, Govindan N. Intracellular biosynthesis of Au and Ag nanoparticles using ethanolic extract of *Brassica oleracea* L. and studies on their physicochemical and biological properties. *J Environ Sci* 2015;29:151-7.
90. Singh J, Upadhyay A, Bahadur A, Singh B, Singh K, Rai M. Antioxidant phytochemicals in cabbage (*Brassica oleracea* L. var. capitata). *Sci Hortic* 2006;108:233-7.
91. Tor YS, Yazan LS, Foo JB, Armania N, Cheah YK, Abdullah R, et al. Induction of apoptosis through oxidative stress-related pathways in MCF-7, human breast cancer cells, by ethyl acetate extract of *Dillenia suffruticosa*. *BMC Complement Altern Med* 2014;14:55.
92. Karimi E, Jaafar HZ, Ahmad S. Antifungal, anti-inflammatory and cytotoxicity activities of three varieties of *labisia pumila* benth: From microwave obtained extracts. *BMC Complement Altern Med* 2013;13:1.
93. Rasool M, Malik A, Manan A, Arooj M, Qazi MH, Kamal MA, et al. Roles of natural compounds from medicinal plants in cancer treatment: Structure and mode of action at molecular level. *Med Chem* 2015;11:618-28.
94. Sathishkumar P, Preethi J, Vijayan R, Mohd Yusoff AR, Ameen F, Suresh S, et al. Anti-acne, anti-dandruff and anti-breast cancer efficacy of green synthesised silver nanoparticles using *Coriandrum sativum* leaf extract. *J Photochem Photobiol B* 2016;163:69-76.
95. Narrima P, Paydar M, Looi CY, Wong YL, Taha H, Wong WF, et al. *Persea declinata* (Bl.) kosterm bark crude extract induces apoptosis in MCF-7 cells via G0/G1 cell cycle arrest, bcl-2/Bax/Bcl-xl signaling pathways, and ROS generation. *Evid Based Complement Alternat Med* 2014;2014:248103.
96. Nassar ZD, Aisha AA, Majid AM. The Pharmacological Properties of Terpenoids from *Sandoricum koetjape*; 2010.
97. Tang EL, Rajarajeswaran J, Fung SY, Kanthimathi MS. Antioxidant activity of *Coriandrum sativum* and protection against DNA damage and cancer cell migration. *BMC Complement Altern Med* 2013;13:347.
98. Hasanzadeh G, Latiffah AL, Hanachi P, Lajis NH. Effect of linoleic acid of *Nigella sativa* on MDA-MB-231 human breast cancer cells. *Iran J Cancer Prev* 2011;4:65-70.
99. Paydar M, Wong YL, Moharam BA, Wong WF, Looi CY. *In vitro* anti-oxidant and anti-cancer activity of methanolic extract from *Sanchezia speciosa* leaves. *Pak J Biol Sci* 2013;16:1212-5.
100. Ho KL, Chung WE, Choong KE, Cheah YL, Phua EY, Srinivasan R. Anti-proliferative activity and preliminary phytochemical screening of *Ipomoea quamoclit* leaf extracts. *Res J Med Plant* 2015;9:127-34.
101. Teoh PL, Ali R, Cheong B. Potential anticancer effect of *Phylla nodiflora* extracts in breast cancer cell line, MCF7. *World J Pharm Pharm Sci* 2013;2:6053-61.
102. Abdullah H, Pihie AH, Hohmann J, Molnár J. A natural compound from *Hydnophytum formicarium* induces apoptosis of MCF-7 cells via up-regulation of Bax. *Cancer Cell Int* 2010;10:14.
103. Muhamad S, Pihie AH, Latif J, Rha C, Sambandan T. Induction of apoptosis in MCF-7 via the Caspase pathway by longilactone from *Eurycoma longifolia* Jack. *Res Pharm Biotechnol* 2011;3:1-10.
104. Looi CY, Arya A, Cheah FK, Muharram B, Leong KH, Mohamad K, et al. Induction of apoptosis in human breast cancer cells via caspase pathway by vernodalin isolated from *Centratherum anthelminticum* (L.) seeds. *PLoS One* 2013;8:e56643.
105. Abu Bakar MF, Mohamad M, Rahmat A, Burr SA, Fry JR. Cytotoxicity, cell cycle arrest, and apoptosis in breast cancer cell lines exposed to an extract of the seed kernel of *Mangifera pajang* (bambangan). *Food Chem Toxicol* 2010;48:1688-97.
106. Ahmad S, Sukari MA, Ismail N, Ismail IS, Abdul AB, Bakar MF, et al. Phytochemicals from *Mangifera pajang* kosterm and their biological activities. *BMC Complement Altern Med* 2015;15:1.
107. Ghil S. Antiproliferative activity of *Alpinia officinarum* extract in the human breast cancer cell line MCF-7. *Mol Med Reports* 2013;7:1288-92.
108. Wong FC, Woo CC, Hsu A, Tan BK. The anti-cancer activities of *Vernonia amygdalina* extract in human breast cancer cell lines are mediated through caspase-dependent and p53-independent pathways. *PLoS One* 2013;8:e78021.
109. Awang K, Azmi MN, Aun LI, Aziz AN, Ibrahim H, Nagoor NH, et al. The apoptotic effect of 1's-1'-acetoxychavicol acetate from *Alpinia conchigera* on human cancer cells. *Molecules* 2010;15:8048-59.
110. Zakaria ZA, Mohamed AM, Jamil NS, Rofiee MS, Hussain MK, Sulaiman MR, et al. *In vitro* antiproliferative and antioxidant activities of the extracts of *Muntingia calabura* leaves. *Am J Chin Med* 2011;39:183-200.
111. Appiah-opong R, Asante IK, Safo DO, Tuffour I, Ofori-attah E, Uto T, et al. Cytotoxic effects of *Albizia zygia* (dc) of macabre, a ghanaian medicinal plant, against human t-lymphoblast-like leukaemia, prostate and breast cancer cell lines. *Int J Pharm Pharm Sci* 2016;8:392-6.
112. Kokila K, Priyadarshini SD, Sujatha V. Phytopharmacological properties of *Albizia* species: A review. *Int J Pharm Pharm Sci* 2013;5:70-3.
113. Ong H, Norzalina J. Malay herbal medicine in Gemencheh, Negri Sembilan, Malaysia. *Fitoterapia* 1999;70:10-4.
114. Sathishkumar P, Vennila K, Jayakumar R, Yusoff AR, Hadibarata T, Palvannan T. Phyto-synthesis of silver nanoparticles using *Alternanthera tenella* leaf extract: An effective inhibitor for the migration of human breast adenocarcinoma (MCF-7) cells. *Bioprocess Biosyst Eng* 2016;39:651-9.
115. Ozsoy N, Yilmaz T, Kurt O, Can A, Yanardag R. *In vitro* antioxidant activity of *Amaranthus lividus* L. *Food Chem* 2009;116:867-72.
116. Roslida A, Fezah O, Yeong L. Suppression of DMBA/croton oil-induced mouse skin tumour promotion by *Ardisia crispa* root hexane extract. *Asian Pac J Cancer Prev* 2011;12:665-9.
117. Hamsin DE, Hamid RA, Yazan LS, Taib CN, Yeong LT. *Ardisia crispa* roots inhibit cyclooxygenase and suppress angiogenesis. *BMC Complement Altern Med* 2014;14:1.
118. Veerakumar S, Amanulla SS, Ramanathan K. Anti-cancer efficacy of ethanolic extracts from various parts of *Annona squamosa* on MCF-7 cell line. *J Pharm Phytother* 2016;8:147-54.
119. Mariod AA, Abdelwahab SI, Elkheir S, Ahmed YM, Fauzi PN, Chuen CS. Antioxidant activity of different parts from *Annona squamosa*, and *Catunaregam nilotica* methanolic extract. *Acta Sci Pol Technol Aliment* 2012;11:249-58.
120. Nguyen MT, Nguyen NT, Awale S. Chapter four-prenylated dihydrochalcones from *Artocarpus altilis* as antiausterity agents. *Enzymes* 2015;37:95-110.
121. Sikarwar MS, Hui BJ, Subramaniam K, Valeisamy BD, Yean LK, Kaveti B. A review on *Artocarpus altilis* (Parkinson) Fosberg (breadfruit). *J Appl Pharm* 2014;4:91-7.
122. Zakaria Z, Rofiee M, Teh L, Salleh M, Sulaiman M, Somchit M. *Bauhinia purpurea* leaves' extracts exhibited *in vitro* antiproliferative and antioxidant activities. *Afr J Biotechnol* 2011;10:65.
123. Balijepalli M, Rou C, Pichika M. Antiproliferative activity of *Bauhinia blakeana* on estrogen receptor negative human breast cancer (MDA-MB-231) cells. *Planta Med* 2010;76:P95.
124. Arbab IA, Abdul AB, Sukari MA, Abdullah R, Syam S, Kamalideghan B, et al. Dentatin isolated from *Clausena excavata* induces apoptosis in MCF-7 cells through the intrinsic pathway with the involvement of NF- κ B signalling and G0/G1 cell cycle arrest: A bioassay-guided approach. *J Ethnopharmacol* 2013;145:343-54.
125. Wong SK, Lim YY, Abdullah NR, Nordin FJ. Assessment of antiproliferative and antiparasmodial activities of five selected *Apocynaceae* species. *BMC Complement Altern Med* 2011;11:1.
126. Thoennissen N, O'Kelly J, Lu D, Iwanski G, La D, Abbassi S, et al. Capsaicin causes cell-cycle arrest and apoptosis in ER-positive and-negative breast cancer cells by modulating the EGFR/HER-2 pathway. *Oncogene* 2010;29:285-96.

127. Jayakumar J, Nirmala P, Kumar BP, Kumar AP. Evaluation of protective effect of myricetin, a bioflavonoid in dimethyl benzanthracene-induced breast cancer in female Wistar rats. *South Asian J Cancer* 2014;3:107.
128. Maisarah A, Asmah R, Fauziah O. Proximate analysis, antioxidant and antiproliferative activities of different parts of *Carica papaya*. *J Nutr Food Sci* 2014;4:1-7.
129. Ismail M, Bagalkotkar G, Iqbal S, Adamu HA. Anticancer properties and phenolic contents of sequentially prepared extracts from different parts of selected medicinal plants indigenous to Malaysia. *Molecules* 2012;17:5745-56.
130. Bidinotto LT, Costa CA, Salvadori DM, Costa M, Rodrigues MA, Barbisan LF. Protective effects of lemongrass (*Cymbopogon citratus* STAPF) essential oil on DNA damage and carcinogenesis in female Balb/C mice. *J Appl Toxicol* 2011;31:536-44.
131. Piaru SP, Perumal S, Cai LW, Mahmud R, Majid AM, Ismail S, et al. Chemical composition, anti-angiogenic and cytotoxicity activities of the essential oils of *Cymbopogon citratus* (lemon grass) against colorectal and breast carcinoma cell lines. *J Essential Oil Res* 2012;24:453-9.
132. Halabi MF, Sheikh BY. Anti-proliferative effect and phytochemical analysis of *Cymbopogon citratus* extract. *BioMed Res Int* 2014;2014:906239.
133. Syed Abdul Rahman SN, Abdul Wahab N, Abd Malek SN. *In vitro* morphological assessment of apoptosis induced by antiproliferative constituents from the rhizomes of *Curcuma zedoaria*. *Evid Based Complement Alternat Med* 2013;2013:257108.
134. Dashora N, ay Sodde V, Prabhu KS, Lobo R. *In vitro* cytotoxic activity of *Dendrophthoe falcata* on human breast acenocarcinoma cells-MCF-7. *Int J Cancer Res* 2011;7:47-54.
135. Zainuddin NA, Sul'ain MD. Phytochemical analysis, toxicity and cytotoxicity evaluation of *Dendrophthoe pentandra* leaves extracts. *Int J Appl Biol Pharm Tech* 2015;6:108-16.
136. Widowati W, Mozef T, Risdian C, Yellianty Y. Anticancer and free radical scavenging potency of *Catharanthus roseus*, *Dendrophthoe pentandra*, *Piper betle* and *Curcuma mangga* extracts in breast cancer cell lines. *Oxid Antioxid Med Sci* 2013;2:137-42.
137. Ting K, Othman M, Telford G, Clarke G, Bradshaw T, Khoo T, et al. Antioxidant, cytoprotective, growth inhibitory and immunomodulatory activities of extracts of *Dysoxylum cauliflorum* Hiern., a Malaysian meliaceae. *J Med Plants Res* 2011;5:5867-72.
138. Chicca A, Adinolfi B, Pellati F, Orlandini G, Benvenuti S, Nieri P. Cytotoxic activity and G1 cell cycle arrest of a dienyne from *Echinacea pallida*. *Planta Med* 2010;76:444-6.
139. Hotel I, Lumpur K. 33rd Annual Conference of the Malaysian Society for Biochemistry and Molecular Biology. Kuala Lumpur: Istana Hotel; 2008.
140. Ho WY, Yeap SK, Ho CL, Raha AR, Suraini AA, Alitheen NB. *Elephantopus scaber* induces cytotoxicity in MCF-7 human breast cancer cells via p53-induced apoptosis. *J Med Plants Res* 2011;5:5741-9.
141. Harun FB, Jamalullail SM, Yin KB, Othman Z, Tilwari A, Balam P. Autophagic cell death is induced by acetone and ethyl acetate extracts from *Eupatorium odoratum* *in vitro*: Effects on MCF-7 and vero cell lines. *Sci World J* 2012;20:1-9.
142. Rosnah J, Khandaker M, Boyce A. *Ficus deltoidea*: Review on Background and recent pharmacological potential. *J Agronomy* 2015;14:310.
143. Artanti N, Hanafi M, Andriyani R, Saraswati V, Udin LZ, Lotulung PD, et al. Isolation of an anti-cancer asperuloside from *Hedyotis corymbosa* L. *J Trop Life Sci* 2015;5:88-91.
144. Lee YK, Lay LK, Mahsufi MS, Guan TS, Elumalai S, Thong OM. Anti-proliferation effect of *Hevea brasiliensis* latex B-serum on human breast epithelial cells. *Pak J Pharm Sci* 2012;25:645-50.
145. Kumkum A, Ranjana V. Inhibition of calcium oxalate crystallization *in vitro* by various extracts of *Hyptis suaveolens* (L.) Poit. *Int Res J Pharm* 2012;3:261-4.
146. Pihie AH, Zakaria ZA, Othman F. Antiproliferative and proapoptotic effects of *Labisia pumila* ethanol extract and its active fraction in human melanoma HM3KO cells. *Evid Based Complement Altern Med* 2012;2012:123470.
147. Al-Mekhlafi NA, Shaari K, Abas F, Kneer R, Jeyaraj EJ, Stanslas J, et al. Alkenylresorcinols and cytotoxic activity of the constituents isolated from *Labisia pumila*. *Phytochemistry* 2012;80:42-9.
148. Kutoi CJ, Yen KH, Seruji NM. Pharmacology evaluation of *Litsea garciae* (Lauraceae). In: *Business Engineering and Industrial Applications Colloquium* (BEIAC): IEEE; 2012. p. 31-33.
149. Garcia-Rivera D, Delgado R, Bougarne N, Haegeman G, Berghe WV. Gallic acid indanone and mangiferin xanthone are strong determinants of immunosuppressive anti-tumour effects of *Mangifera indica* L. Bark in MDA-MB231 breast cancer cells. *Cancer Lett* 2011;305:21-31.
150. Roslen NA, Alewi NA, Ahamada H, Rasad MS. Cytotoxicity screening of *Melastoma malabathricum* extracts on human breast cancer cell lines *in vitro*. *Asian Pac J Trop Biomed* 2014;4:545-8.
151. Khalafalla MM, Abdellatef E, Dafalla HM, Nassrallah AA, Aboul-Enein KM, Lightfoot DA. Active principle from *Moringa oleifera* Lam leaves effective against two leukemias and a hepatocarcinoma. *Afr J Biotechnol* 2010;9:8467.
152. Ghasemzadeh A, Jaafar HZ, Rahmat A, Devarajan T. Evaluation of bioactive compounds, pharmaceutical quality, and anticancer activity of curry leaf (*Murraya koenigii* L.). *Evid Based Complement Altern Med* 2014;2014. Article ID 873803.
153. Sayar K, Paydar M, Pinguun-Murphy B. Pharmacological properties and chemical constituents of *Murraya paniculata* (L.) Jack. *Med Aromat Plants* 2014;3:173.
154. Basheer MK, Majid AM. Medicinal Potentials of *Orthosiphon stamineus* Benth. *WebmedCentral Cancer* 2010;1:WMC0013612010.
155. Ooi DJ, Iqbal S, Ismail M. Proximate composition, nutritional attributes and mineral composition of *Peperomia pellucida* L. (Ketumpangan Air) grown in Malaysia. *Molecules* 2012;17:11139-45.
156. Wei LS, Wee W, Siong JY, Syamsumir DF. Characterization of anticancer, antimicrobial, antioxidant properties and chemical compositions of *Peperomia pellucida* leaf extract. *Acta Med Iran* 2011;49:670.
157. Hendra R, Ahmad S, Oskoueian E, Sukari A, Shukor MY. Antioxidant, anti-inflammatory and cytotoxicity of *Phaleria macrocarpa* (Boerl.) scheff fruit. *BMC Complement Altern Med* 2011;11:1.
158. Ee GC, Lim CM, Rahmani M, Shaari K, Bong CF. Pellitorine, a potential anti-cancer lead compound against HL60 and MCT-7 cell lines and microbial transformation of piperine from *Piper nigrum*. *Molecules* 2010;15:2398-404.
159. Sul'ain MD, Zazali KE, Ahmad N. Screening on anti-proliferative activity of *Psidium guajava* leaves extract towards selected cancer cell lines. *J US China Med Sci* 2012;9:30-7.
160. Masaud IA, Baig AA, Rohin MA, Mohamad N. Potential of therapeutic antioxidant compounds from pomegranate as anti-cancer agent. *J Chem Pharm Res* 2014;6:427-33.
161. Kim KH, Kim CS, Park YJ, Moon E, Choi SU, Lee JH, et al. Anti-inflammatory and antitumor phenylpropanoid sucrosides from the seeds of *Raphanus sativus*. *Bioorg Med Chem Lett* 2015;25:96-9.
162. Hu X, Zhang X, Qiu S, Yu D, Lin S. Salidroside induces cell-cycle arrest and apoptosis in human breast cancer cells. *Biochem Biophys Res Comm* 2010;398:62-7.
163. Rahmat A, Edrini S, Ismail P, Yap T, Hin Y, Bakar MA. Chemical constituents, antioxidant activity and cytotoxic effects of essential oil from *Strobilanthes crispus* and *Lawsonia inermis*. *J Biol Sci* 2006;6:1005-10.
164. Ibahim M, I'zzah WN, Narimah A, Asyikin NZ, Shafinas SN, Froemming G. Anti-proliferative and antioxidant effects of *Tinospora crispa* (Batawali). *Biomed Res India* 2011;22:57-62.
165. Bhagat N, Chaturvedi A. Spices as an alternative therapy for cancer treatment. *Syst Rev Pharm* 2016;7:46-56.
166. Ayob Z, Samad AA, Bohari SP. Cytotoxicity activities in local *Justicia gendarussa* crude extracts against human cancer cell lines. *J Teknol* 2013;64:45-52.
167. Ling AL, Yasir S, Matanjun P, Bakar MF. Effect of different drying techniques on the phytochemical content and antioxidant activity of *Kappaphycus alvarezii*. *J Appl Phycol* 2015;27:1717-23.
168. Baharum Z, Akim AM, Taufiq-Yap YH, Hamid RA, Kasran R. *In vitro* antioxidant and antiproliferative activities of methanolic plant part extracts of *Theobroma cacao*. *Molecules* 2014;19:18317-31.
169. Nurrochmad A, Lukitaningsih E, Meiyanto E. Anti cancer activity of rodent tuber (*Thyphonium flagelliforme* (Lodd.) Blume on human breast cancer t47d cells. *Int J Phytomed* 2011;3:138.
170. Mohan S, Abdul AB, Abdelwahab SI, Al-Zubairi AS, Sukari MA, Abdullah R, et al. *Typhonium flagelliforme* induces apoptosis in CEMss cells via activation of caspase-9, PARP cleavage and cytochrome c release: Its activation coupled with G0/G1 phase cell cycle arrest. *J Ethnopharmacol* 2010;131:592-600.
171. Srisawat T, Chumkaew P, Heed-Chim W, Sukpondma Y, Kanokwiroon K. Phytochemical screening and cytotoxicity of crude

- extracts of *Vatica diospyroides* symington type LS. Trop J Pharm Res 2013;12:71-6.
172. Biswal BM, Sulaiman SA, Ismail HC, Zakaria H, Musa KI. Effect of *Withania somnifera* (Ashwagandha) on the development of chemotherapy-induced fatigue and quality of life in breast cancer patients. Integr Cancer Ther 2013;12:312-22.
173. Ghasemzadeh A, Jaafar HZ. Antioxidant potential and anticancer activity of young ginger (*Zingiber officinale* Roscoe) grown under different CO₂ concentration. J Med Plants Res 2011;5:3247-55.
174. Raghavendra L, PrashithKekuda R. Ethnobotanical uses, phytochemistry and pharmacological activities of *Peperomia pellucida* (L.) Kunth (piperaceae)-a review. Int J Pharm Pharm Sci 2018;10:1-8.
175. Shamsi T, Parveen R, Sajida A, Ahmad A, Fatima S. Assessing the therapeutic role of joshanda: Phytochemical, antioxidant, anti-inflammatory and antimicrobial activities. Int J Pharm Pharm Sci 2018;10:122-8.