REVIEW ARTICLE

Phytochemicals Constituents of Malay Traditional Medicinal Plants as Potential Remedies for Breast Cancer: A Review

Raja Siti Syazana Raja Soh[1], Mohammad Syaiful Bahari Abdull Rasad [1,*]

[1]Department of Biomedical Sciences, Kulliyyah of Allied Health Sciences, International Islamic University Malaysia, Pahang, Malaysia

Keywords:
Malay traditional medicinal plants; phytochemical; anti-breast cancer; remedies

ABSTRACT

Background: Breast cancer is the most prominent cancer in Malaysia, followed by lung, nasopharyngeal, colorectal, and liver cancers. Data from the World Health Organisation (2020) support the nation's high incidence of breast cancer. Studies have shown that phytochemicals, or secondary plant metabolites, have a promising future as adjuvants for a number of current medicines. The aim of this research is to provide an overview of the phytochemical components identified in traditional Malay medicinal plants that may be used to treat breast cancer in Malaysian women. **Methods**: The most prominent phytochemicals found Malay traditional medicinal plants with anticancer activities against breast cancer are identified and compiled using a scoping review technique. Scopus, ScienceDirect, and PubMed were the three databases used in the study to search for papers that fit the inclusion and exclusion criteria. The screening approach concentrates on English papers from January 2015 to April 2023, utilising keywords such as the scientific names of the 45 identified plants, "phytochemical," and "breast cancer". **Results**: Out of 702 screened articles, only 23 met the predetermined criteria and were included in the study. The analysis reveals that 13 Malay traditional medicinal plants show positive outcomes against breast cancer, primarily due to the presence of phenolic compounds in their extract. **Conclusions**: The study identifies 13 out of 45 selected Malay traditional medicinal plants that exhibit positive outcomes against breast cancer. These plants contain significant phytochemicals such as phenolic compounds, alkaloids, terpenoids, and others, highlighting their potential as therapeutic agents. This comprehensive review is expected to assist researchers in embarking on pre-clinical studies focused on potential Malay traditional plants for breast cancer treatment and further elucidating the pharmacology of these phytomedicines.

INTRODUCTION

According to the World Health Organization, breast cancer recorded the highest number of new cases in 2020 at approximately 2.26 million cases, followed by lung, colon and rectum cancer and prostate cancer. In addition, breast cancer statistics worldwide also indicate quite a high number of cancer mortality rates in 2020. Additionally, breast cancer is the most prevalent type of cancer in Malaysia, followed by colorectal, lung, nasopharyngeal, and liver cancers (WHO, 2020). One of the leading causes of mortality for cancer-stricken Malaysian women is breast cancer, followed by cervical cancer. Various types of therapies, such as chemotherapy, immunotherapy, and radiation therapy, are used in treating cancer accompanied by severe side effects for the patients who undergo it (Iqbal et al., 2017). Due to its known long-term adverse effects on the patient, a new approach was made for a safer chemotherapeutic design.

Iqbal et al. (2017) expressed that plant-derived products are eco-friendly, safer, affordable, and less hazardous compared to allopathic medicine or mainstream medicine. Research into phytochemicals, especially phenolic compounds and flavonoids, reveals their potential in combating oxidative stress and preventing cancer, underscoring the importance of exploring these natural compounds for safer, more effective breast cancer therapiesas reported by Mainasara et al. (2018).Several published articles also suggested the potential of phenolic compounds as antioxidants against oxidative stress disease in humans (Kikuchi et al., 2019; Luna-Guevara et al., 2018; Younas et al., 2018). For instance, a review by Younas et al. (2018) that focuses on phytochemical compounds, especially the flavonoid groups, gives a vital knowledge of the mechanisms for each compound in breast cancer chemoprevention. Phytochemicals such as curcumin, resveratrol, epigallocatechin gallate (ECGCG), silibinin, benzyl isothiocyanate, genistein, kaempferol and quercetin have been shown to restrict breast cancer in a few mechanisms of action.

A compilation of 45 Malay traditional medicinal plants is listed in supplementary materials. The list is mainly

* *Corresponding author.*
E-mail address: syaiful@iium.edu.my

extracted from Abuga et al. (2022). The list was adopted for a more thorough scoping assessment in this study on the effectiveness of anticancer against breast cancer. Zakaria (2010) mentioned that Malay traditional medicine passed on information about treatments and supplies verbally and via memory. As a result, knowledge of Malay traditional medicine that has high nutritional and health benefits to humans must be documented to ensure its validity and preservation (Zakaria, 2010).

The objective of this review is to assess the anticancer potential of specific phytochemicals found in these plants through a comprehensive analysis of peer-reviewed scientific literature. Compiling these phytochemicals provides valuable insights into their potential anticancer properties against breast cancer.

MATERIALS AND METHODS

Study design

This scoping review was accomplished based on the Population, Intervention, Comparison, Outcomes (PICO) design, as shown in Table 1, which was used to compose the eligibility criteria in the scoping review and as a framework to develop research questions. In addition, a flow diagram for Preferred Reporting Items for Systematic and Meta-analyses extension for Scoping Review, PRISMA-ScR by Tricco et al. (2018) was adopted, which consists of identification, screening, eligibility, and the included article (Figure 1).

Table 1: PICO framework

Criteria	Determinants
Problem	Breast cancer and Malay traditional medicinal plants.
Interest	Anticancer activity and phytochemicals.
Comparison	Not applicable.
Outcomes	**Primary outcome**: Identification of Malay traditional medicinal plants as anti-breast cancer. **Secondary outcome**: List of phytochemicals in selected Malay traditional medicinal plants.

Identifying the research question

The review questions were: (1) Which plants among the published list of 45 Malay traditional medicinal plants from Abuga et al. 2022 have sufficient published reports of anticancer activity against breast cancer? (2) What are the phytochemicals found in the selected plants that have breast anticancer?

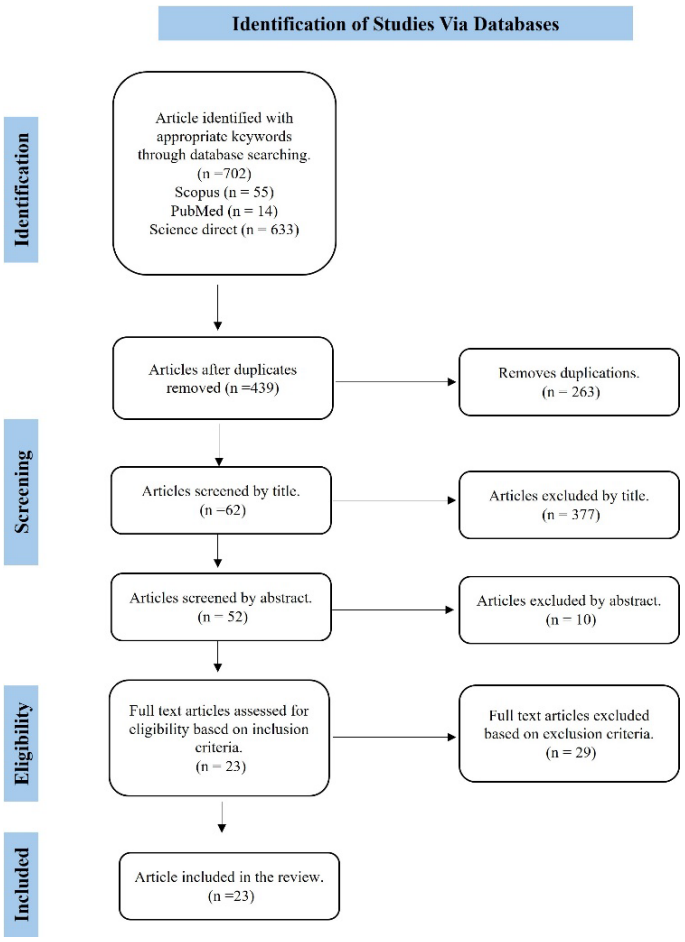

Figure 1: Flow diagram of study selection

Search strategy

Scopus, Science Direct, and PubMed databases wereutilized and screened for the related articles that matched the keywords and studies reported from December 2022 until April 2023. The keywords used were "name of scientific plants", "phytochemical" and "breast cancer". The Boolean terms 'AND' are used to combine the keywords. For instance, "*Adenosterma viscosum*" AND "Breast cancer" AND "phytochemical".

Data selection and collection

Inclusion and exclusion criteria in selecting the article throughout the research project are listed in Table 2.

Charting the data

The findings are summarized based on the authors' names, publication year, plant names, plant parts, extraction solvent, extraction method, *in vivo* or *in vitro* studies, pure compounds or crude extracts, specific phytochemical compounds, human breast cell lines used, and positive outcomes on breast cancer as shown in Table 3.

Table 2: Inclusion and exclusion criteria

Inclusion	Exclusion
• Article from 2015 onwards. • The language uses English. • Full text accessible. • Qualitative and quantitative study for all breast cancer types, pure compound, and crude extract. • Experimental study for both *in vivo* and *in vitro.* • Index paper.	• Review study, discussion, book chapter, survey, questionnaire and others. • Chemically synthesized phytochemical.

RESULTS

Overview of identified articles

Initially, 702 items matching the criteria were found in three databases: 55 articles in Scopus, 14 in PubMed, and 633 in Science Direct, as shown in Figure 1. The articles were subsequently uploaded into Mendeley to be reviewed and duplicated between the three databases removed. 263 duplicate articles were deleted, and the remaining 439 were screened further based on their title. Following the removal of 377 articles, 62 articles were reviewed based on their abstracts. After examining the abstract, 52 papers were left. To choose the 23 included articles, full-text accessibility and eligibility based on inclusion and exclusion criteria were utilized.

Phytochemical as anticancer

A list of phytochemicals from 13 selected Malay traditional medicinal plants was tabulated in Table 4 to achieve the primary objective of this study.

Table 4: List of phytochemicals found in Malay traditional medicinal plants that exhibited anticancer properties against the breast.

Scientific name of plants	Phytochemicals
Allium sativum	• Thiosulfonate • Flavonoids • Terpenoids • Alkaloids • Allicin
Cinnamomum verum	• Benzoic acid, cinnamic acid, flavonoid • Oxygenated monoterpenes • Sesquiterpene hydrocarbons • Oxygenated sesquiterpenes • Phenylpropanoids
Curcuma longa	• Phenolic, flavonoid, condensed tannin, hydrolysable tannin • Curcumin, quercetin, epicatechin
Lagerstroemia speciosa	• Flavonoids • (Gallic acid, quercetin)
Momordica charantia	• 3β,7β,25-trihydroxycucurbita-5,23(E)-dien-19-al (TCD) • 10% alkaloid • 4% phenols • 7% tannins • 1% flavonoid • 6% saponin
Murraya koenigii	• Alkaloids • Triterpenoids • Flavonoids • Tannins • Phenols • Mahanine (MH)
Ocimum basilicum	• Linalool • Eugenol • Geraniol • Methyl-chavicol • Phenolics • Flavonoids
Phyllanthus emblica	• Alkaloids • Phenol • Flavonoids • Saponins
Psidium guajava	• Guajadial • Triterpenoids • Flavonoids • Psidial A
Punica granatum	• Octadecatrienoic acid • Sterols • Steroids (17-α Estradiol, tocol, γ-tocopherol) • Terpenes, Sesquiterpenes • Polyphenolic, flavonoids, tannic acid and gallic acid derivatives • Fatty acid (punicic acid highest)
Quercus infectoria	• Terpenoids • Phenols • Alkaloids
Tamarindus indica	• Phenols (flavonoid)
Zingiber officinale	• 6-shagoal • [10]-gingerol • [8]-gingerol • [6]-gingerol

Table 3: Extraction data from the accepted article that match the inclusion criteria (n=23).

Authors' name & year	Name plants	Parts of plants	Extraction solvent	Extraction method	*In vivo/ in vitro*	Pure compound/ crude extract	Phytochemical compound	Human breast cell line/ animal model	Positive outcome
(Bai et al., 2016)	*Momordica charantia*	Whole parts	-	-	*In vitro*	Pure	3β,7β,25-trihydroxycucurbita-5,23(E)-dien-19-al (TCD)	• MCF-7 • MDA-MB-231	• Suppress the antiproliferative of breast cancer lines. • HDAC inhibition. • Induce apoptosis through ROS generation. • Downregulation of Akt-NF-kB signalling • Activation of p53 phosphorylation
(Kilcar et al., 2020)	*Momordica charantia*	Seeds	80% ethanol	Reflux extraction	*In vitro*	Crude	10% alkaloid 4% phenols 7% tannins 1% flavonoid 6% saponin	• MCF-7 (ER+) • MDA-MB-231 (ER-)	• Incubation of cells with bitter melon extract (BME) raised paclitaxel (PAC) IC_{50} value.
(Al-Zereini et al., 2022)	*Cinnamomum verum*	Bark	Distilled water	Hydro-distilled	*In vitro*	Crude essential oils (EO)	Oxygenated monoterpenes Sesquiterpene hydrocarbons Oxygenated sesquiterpenes Phenylpropanoid Others	• MDA-MB-231	• Inhibit tumour cells proliferation with IC_{50} 0.14µl/mL
(Guneidy et al., 2022)	*Curcuma longa* *Zingiber officinale* *Syzygium aromaticum* *Tamarindus indica* *Cinnamomum verum* *Punica granatum*	Rhizome Rhizome Seed Seed Bark Seed	70% of solvent (acetone / ethanol)		*In vitro*	Crude	Phenolic, flavonoid, condensed tannin, hydrolysable tannin Benzoic acid, cinnamic acid, flavonoid Phenolic, flavonoid, condensed tannin, hydrolysable tannin, anthocyanins	• MCF-7	• Only *Tamarindus indica* and *Cinnamomum verum* showed cytotoxicity effects.

(Ali et al., 2022)	*Zingiber officinale Rosc*	Rhizomes	Petroleum ether (PE) and chloroform: methanol (CM)	maceration	*In vitro*	Pure	6-gingerol 6-shogaol	• MCF-7	• Cytotoxicity effect.
(Meysami et al., 2021)	*Zingiber officinale Roscoe*	Rhizomes	70% ethanol	maceration	*In vivo*	Pure	6- gingerol	• Mice, inject with 4T1	• Downregulated of specific oncogenes (MMP-13)
(Lucci et al., 2015)	*Punica granatum*	Whole seed	Absolute ethanol	-	*In vitro*	Crude	Phenolic compound Fatty acid (punicic acid highest)	• MCF-7	• Promising antiproliferative activity with IC_{50} value 26.5 μg/ml.
(Nadaf et al., 2020)	*Murraya koenigii*	Seed	Methanol	Soxhlet	*In vitro*	Crude	Alkaloids Triterpenoids Flavonoids Tannins Phenols	• MCF-7	• Cell viability significantly reduced compared to control
(Bazioli et al., 2020)	*Psidium guajava*	leaves	Dichloromethane	-	*In vitro* *In vivo*- hollow fiber assay	Crude	Flavonoids Triterpenoids Phenolics Meroterpenoids-Guajadial (49%) Psidial A	• MCF-7 • MCF-7 BUS • Swiss female mice, Balb-C female mice, Wistar female mice	• Successive fractionation shows potent antiproliferative activity on MCF-7, MVF-7 BUS • Tumour inhibition through estrogen receptors (*in vivo)*
(Alkhateeb et al., 2021)	*Ocimum basilicum*	Fresh blossoms	Water	Aqueous extract	*In vitro*	Crude	Phenolic Flavonoids	• MCF-7	• Restrains development and multiplication of breast cancer through apoptotic.
(Durgawale & Datkhile, 2016)	*Punica granatum*	Flowers	Methanol	Maceration	*In vitro*	Crude	Polyphenolic Flavonoids Tannic acid and gallic acid derivatives	• MCF-7	• Positive anti-cancer activity on MTT anti proliferative assay
(Wan Yusof & Abdullah, 2020)	*Quercus infectoria*	Galls	n-hexane ethyl acetate methanol	maceration	*In vitro*	Crude	Tannins Alkaloids Saponin Terpenes Flavonoids Glycosides Phenolic compound	• MCF-7 • MDA-MB-231	• High toxicity for MCF-7 on ethyl acetate extract with the lowest IC_{50} value. • Methanolic extract of *Quercus infectoria* has high cytotoxicity on MDA-MB-231.

(Sai Saraswathi, Rajaguru, et al., 2017)	*Lagerstroemia speciosa*	Leaves	Acetone Methanolic	Soxhlet	*In vitro*	Crude	Gallic acid (check use HPTLC) Flavonoids	•	MCF-7	• Acetone extract displayed significant cytotoxicity activity on breast cells.
(Yang et al., 2020)	*Curcuma longaz*	Rhizomes	Ethanol (80%)	Ultrasonic assisted extraction (UAE) Conventional solvent extraction (CSE)	*In vitro*	Crude	Phenolic compounds (Curcumin, quercetin, epicatechin, etc.)	• •	MCF-7 MDA-MB-231	• UAE showed higher phenolic compound and cytotoxicity activity on breast cancer lines.
(Sai Saraswathi, Saravanan, et al., 2017)	*Lagerstroemia speciosa*	Leaves	Methanolic	Soxhlet	*In vitro*	Pure Crude	Quercetin (isolated using HPLC)	•	MCF-7	• Pure compound quercetin showed higher cytotoxicity and cell viability than methanolic crude extract.
Elgndi et al., 2017	*Ocimum basilicum*	Leaves	Carbon dioxide	Supercritical fluid extraction (SFE) Hydro distillation (essential oil)	*In vitro*	Crude	Linalool Eugenol Geraniol Methyl-chavicol	•	MDA-MB-453	• Antioxidant and antiproliferative activity of EO and CO_2 extract but significantly higher antioxidant activity in EO.
(Das et al., 2019)	*Murraya koenigii*	Leaves	Methanol	Cold maceration	*In vitro* *In vivo*	Pure	Mahanine (isolated using HPLC)	• • •	MCF-7 MDA-MB-231 N-methyl-N-nitrosourea (MNU) induced rat	• Reduce proliferation through apoptosis both on MCF-7 and MDA-MB-231. • Reduced mammary tumour weight in MNU induced rat.
(Zheng et al., 2018)	*Phyllanthus acidus*	Stems and roots	Methanol	Reflux	*In vitro*	Pure	Cleistanthane diterpenoids; phyllaciduloids A-D	•	MCF-7	• No obvious activity at a concentration of 40μM.
(Talib, 2017)	*Allium sativum*	Bulbs	Aqueous	-	*In vivo*	Crude	Thiosulfonate Flavonoids Terpenoids Alkaloids Allicin	•	Balb/c female mice	• 60% undetectable tumours were reported for mice treated with garlic extract, but the combination of garlic and lemon was reported for 80%.

(Mónica et al., 2020)	*Punica granatum*	Seeds and peels	Ethanol Chloroform Hexane	-	*In vitro*	Crude	Terpenes, Sesquiterpenes Flavonoids Steroid	• MDA-MB-231	• Seed extract showed cytotoxicity activity.
(Patel et al., 2022)	*Phyllanthus emblica*	Fruits	Chloroform Ethyl acetate Methanol Ethanol Distilled water	Series extraction method	*In vitro*	Crude	Alkaloids Phenol Flavonoids Saponins	• MCF-7	• Aqueous extract reported decreased cell viability as concentration increased.
(Mandal et al., 2015)	*Punica granatum*	Seed oil and aqueous extract (PE emulsion)	-	-	*In vivo*	Crude	Octadecatrienoic acid Sterols Steroids (17-α Estradiol, tocol, y-tocopherol)	• 7,12-dimethylbenz[α]anthracene (DMBA) induced rats	• Decrease ER- α and ER- β expression in mammary tumour.
(Bernard et al., 2017)	*Zingiber officinale*		-	-	*In vitro*	Pure	[10]-gingerol [8]-gingerol [6]-gingerol	• MDA-MB-231 • MDA-MB-468	• Inhibitory of TNBC growth.

Notes: CM, chloroform methanol; DMBA, 7,12-dimethylbenz[α]anthracene; ECGC, epigallocatechin gallate; ER, estrogen receptor; HT116, colon adenocarcinoma; HeLa, human cervical cancer cell line; HepG2, human hepatoma; HPLC, high performance liquid chromatography; HT29, colon adenocarcinoma; MH, mahanine; MCF-7, human mammary cancer cells; MDA-MB-231, triple-negative breast cancer cell line; MNU, N-methyl-N-nitrosourea; PE, petroleum ether.

In earlier studies, it was discovered that the traditional Malay remedies reported had antioxidant and anticancer characteristics that extended beyond breast cancer. For instance, mahanine (MH) a compound extracted from *Murraya koenigii* has lately gained attention as a possible candidate to prevent several cancers, including leukemia, pancreas, cervix, lungs, colorectal, prostate, and glioma (Das et al., 2019).

Besides that, the cytotoxicity impact of C*urcuma longa* extract on a few cancer cell lines (MCF7, MDA-MB-231, HCT116, HT29, HepG2, HeLa) was also reported by Yang et al. (2020) research, demonstrating its anticancer properties. Meanwhile, Monica et al. (2020) studies demonstrated *Punica granatum's* anticancer properties as the ethanolic seed extract had a cytotoxic effect on the cancer cell lines MDA-MB231 and HT29. Furthermore, Durgawale & Datkhile (2016) revealed that the methanolic flower extract of *Punica granatum* had anti-proliferative effects against all three cancer cell lines they studied, which were derived from breast, liver, and cervical cancer types. According to Ali et al. (2022), the HT29, HCT116, and MCF-7 cancer cell lines were all sensitive to ginger rhizome petroleum ether (PE) and chloroform; methanol (CM) extracts, with CM extract having the most significant cytotoxicity effect.

Both *Curcuma longa,* and *Punica granatum* extract consist of phenolic compounds that act as anticancer on MCF-7 cell lines. However, secondary metabolites in *Curcuma longa* extract, curcumin, also have anticancer activity, as reported by Yang et al. (2020). On the other hand, a pure extract of mahanine from *Murraya koenigii* has a significant effect as an anticancer in both *in vitro* and *in vivo*. A pure extract from the rhizome of *Zingiber officinale* also proved its anticancer activity due to the presence of 6-gingerol and 6-shagoal.

In summary, extracts from *Curcuma longa, Punica granatum, Murraya koenigii,* and *Zingiber officinale* contain phenolic compounds and secondary metabolites with notable anticancer effects on various human cancer cell lines, including MCF-7. Curcumin in *Curcuma longa*, mahanine in *Murraya koenigii*, and 6-gingerol and 6-shogaol in *Zingiber officinale* have each shown potent anticancer properties in both *in vitro* and *in vivo* studies. Further research into these phytochemicals, especially their effects on specific cancer types, could enhance drug development efforts by identifying promising candidates for targeted anticancer therapies.

Plant extract effect on breast cancer

According to Table 3, *Punica granatum* was the plant that was mentioned in relation to breast cancer the most often out of the 23 papers that were accepted (Lucci et al., 2021; Durgawale & Datkhile, 2016; Monica et al., 2020; Mandal et al., 2015). In all breast cancer investigations, anti-proliferative activity was shown to be promising on MCF-7 (Lucci et al., 2021), anti-proliferative in 7,12-dimethylbenz[α]anthracene (DMBA) rats (Mandal et al., 2015), and seed extract showed cytotoxicity impact (Monica et al., 2020; Durgawale & Datkhile, 2016). However, *Zingiber officinale,* the second-most frequently suggested plant, reported a pure product of 6-gingerol, and 6-shagoal from rhizome extract (Ali et al., 2022). The efficacy of [10]-gingerol, [8]-gingerol, and [6]-gingerol to suppress the growth of human and mouse mammary cancer cells was compared by Bernard et al. (2017).

In addition, according to extraction data, all plants were evaluated on human cancer cell lines aside from *Psidium guajava* and *Murraya koenigii*, which were examined on both cell lines and animal models. According to Bazioli et al. (2020), *Psidium guajava* (guajadial, terpenoid, polyphenol) has substantial antiproliferative activity on MCF-7, MCF-7 BUS, and tumor inhibition via estrogen receptors. It also exhibited beneficial results in both *in vivo* and *in vitro* experiments. Due to polyphenolic components and terpenoids in the crude extract, *Murraya koenigii* methanolic extract also favorably affected MCF-7 (Nadaf et al., 2020). The *in vivo* and *in vitro* results of investigations utilizing the MCF-7, MDA-MB-231, and N-methyl-N-nitrosourea (MNU) rat strains of pure extracted mahanine by HPLC were favorable (Das et al., 2019).

DISCUSSION

Mechanism of action of phytochemicals from various plant extracts

Punica granatum

After an extensive literature review, this study highlights the findings of Mandal et al. (2015), which demonstrated positive outcomes in breast cancer treatment using pomegranate emulsion (PE). The chemical analysis of pomegranate formulation revealed that the lipid phase contained mixed octadecatrienoic acids, sterols, and steroids, particularly 17-α-estradiol, as well as tocol and γ-tocopherol, and the aqueous phase contained caffeic acid, corilagin, ellagic acid, ferulic acid, gallic acid, 5-hydroxymethylfurfural, protocatechuic acid, punicalagin alpha and punicalagin beta. Mandal et al. (2015) proposed that pomegranate emulsion (PE) inhibited cell proliferation, induced apoptosis, upregulated proapoptotic protein Bax, and downregulated antiapoptotic protein Bcl-2 in mammary tumors in DMBA-

initiated rats. These effects were associated with decreased incidence, total burden, and average weight of mammary tumors. Not only that, in Mandal et al. (2015) investigation, the author also looked at the expression of ER-α and ER-β in rats given PE therapy and DMBA-induced mammary tumours.

The findings show that ER-α and ER-β are expressed significantly in mammary tumours eradicated in DMBA control animals. The findings are intriguingly consistent with a prior study that showed that a methanolic extract of pomegranate pericarp (peel) prevented estradiol binding to ER, downregulated the ER-α gene, and decreased the growth and proliferation of ER-positive MCF-7 breast cancer cells (Sreeja et al., 2012).

Additionally, a recent review study from Moga et al. (2021) explored the anticancer mechanism and molecular targets of *Punica granatum*, focusing on the main phenolic chemicals detected in the peels, juice and seeds extract, demonstrating that pomegranates are a possible therapy option for breast cancer. Furthermore, ellagic acid, punicic acid, ellagitannins, anthocyanins and anthocyanidins, flavones, flavonoids, and estrogenic flavonols are the most prominent therapeutically active polyphenols from pomegranates.

Murraya koenigii

Nadaf et al. (2020) concluded that the methanolic extract of Murraya koenigii seeds (MEMS) displayed an antiproliferative impact primarily by inducing apoptosis, which included depolarizing the mitochondrial membrane and activating caspase. It has the antioxidant capacity to demonstrate cytotoxicity by acting as an oxidant scavenger and lowering oxidative stress. Furthermore, it was discovered that MEMS activated caspase activity in a concentration-dependent way. A further dosage form design requires thorough investigation.

On the other hand, mahanine, a pure substance from *Murraya koenigii*, has already demonstrated its promise as a cervical, lung, prostate, and glioma inhibitor (Samanta et al., 2018). Therefore, it piques interest to learn more about its anticancer effects on breast cancer. It was confirmed by Samanta et al. (2016) that administering MH at a dose of 50 mg/kg body weight three times per week for four weeks has the capacity to completely eliminate tumour incidence and mammary tumour volume. The current study's findings from Das et al. (2019) also demonstrated that the naturally occurring carbazole alkaloid MH is highly efficient at lowering breast cancer subtypes independent of cell proliferation through inhibition of breast cancer stem cell (bCSC) population and *in vivo* suppression of mammary tumour burden in MNU-induced breast cancer.

Therefore, the methanolic extract of *Murraya koenigii* seeds (MEMS) shows strong antiproliferative and antioxidant properties by promoting apoptosis and reducing oxidative stress. Additionally, MEMS activates caspase in a concentration-dependent manner, suggesting further investigation into optimized dosage forms. Furthermore, mahanine, a pure compound from *Murraya koenigii*, has shown promise in inhibiting various cancers, including breast cancer. Studies demonstrate that mahanine effectively reduces breast cancer cell populations and tumor burden, emphasizing the potential of *Murraya koenigii* in both its crude and purified forms as an anti-breast cancer agent.

Momordica charantia

Cucurbitane-type triterpenoids, cucurbitane-type triterpene glycosides, phenolic acids, flavonoids, essential oils, fatty acids, amino acids, lectins, sterols, saponin (goyasaponins I, II, and III) constituents, as well as some proteins present in fruits, seeds, roots, leaves, and vines, are the main chemical components of bitter melon that give it biological activity (Dandawate et al., 2016).

The triterpenoid 3β,7β,25-trihydroxycucurbita-5,23(E)-dien-19-al (TCD) inhibited the growth of MCF-7 and MDA-MB-231 breast cancer cells in a PPARγ-independent manner, with IC_{50} values at 72 hours of 19 and 23 M, respectively. TCD-induced cell apoptosis, along with a variety of biological modifications, such as the inhibition of histone deacetylase protein expression, downregulation of Akt-NF-B signalling, upregulation of p38 mitogen-activated protein kinase and p53, and cytoprotective autophagy (Bai et al., 2016). Moreover, a study by Sur et al. (2020) recorded the bitter melon as a promising cancer prevention and therapeutic agent for several types of cancer. The therapeutic effect of the phytochemicals extracted from the bitter melon was recorded in Table 5. *Punica granatum* was discussed because it was frequently mentioned in four of 23 accepted articles. Meanwhile, pure compounds from *Murraya koenigii* and *Momordica charantia* were also discussed. However, the other ten plants, whose mechanisms of action were not discussed, also have potential remedies for breast cancer.

CONCLUSION

The study indicates that several Malay traditional medicinal plants have anti-breast cancer effects. *Allium sativum, Cinnamomum verum, Curcuma longa, Lagerstroemia speciosa, Momordica charantia, Murraya koenigii, Ocimum basilicum, Phyllanthus emblica, Psidium*

Table 5: Bitter melon compound therapeutic effect on breast cancer (Source: Sur et al. 2020)

Cancer	Bitter melon extract/compound	Therapeutic effect
Breast	Water extract of fruit, dried extract and isolated compounds 3β,7β,25-trihydroxycucurbita-5,23(E)-dien-19-al (TCD), eleostearic acid, RNase MC2, MAP30	Inhibited breast cancer cells growth, induced apoptosis and autophagy Inhibited syngenic tumor, xenograft tumor and spontaneous mammary tumorigenesis in SHN virgin mice

guajava, Punica granatum, Quercus infectoria, Tamarindus indica, and *Zingiber officinale* are among the notable plants. This study also discovered that these 13 Malay traditional medicinal plants contain a variety of phytochemicals, including mahanine (MH), guajadial, 6-gingerol, 6-shogaol, and other polyphenolic compounds, alkaloids, terpenoids, and sterols. The anticancer capabilities of these substances have been proven in earlier studies using breast cancer cell lines and animal models.

ACKNOWLEDGEMENT

This research was not funded by any grant.

REFERENCES

Abuga, I., Sulaiman, S. F., Abdul Wahab, R., Ooi, K. L., & Abdull Rasad, M. S. B. (2022). Phytochemical constituents and antibacterial activities of 45 Malay traditional medicinal plants. *Journal of Herbal Medicine*, *32*. https://doi.org/10.1016/j.hermed.2021.100496

Ali, A. M. A., El-Nour, M. E. M., Yagi, S. M., Qahtan, A. A., Alatar, A. A., Abdel-Salam, E. M., & Zengin, G. (2022). Cytotoxicity, phytochemical screening and genetic analysis of ginger (*Zingiber officinale Rosc*.) Callus and Rhizome. *South African Journal of Botany*, *151*, 54–59. https://doi.org/10.1016/j.sajb.2021.11.011

Bai, L.Y., Chiu, C.-F., Chu, P.-C., Lin, W.-Y., Chiu, S.-J., & Weng, J.-R. (2016). A triterpenoid from wild bitter gourd inhibits breast cancer cells. Scientific Reports, 6. https://doi.org/10.1038/srep22419

Bazioli, J. M., Costa, J. H., Shiozawa, L., Ruiz, A. L. T. G., Foglio, M. A., & de Carvalho, J. E. (2020). Anti-estrogenic activity of guajadial fraction, from guava leaves (*Psidium guajava* L.). *Molecules*, *25*(7). https://doi.org/10.3390/molecules25071525

Bernard, M. M., McConnery, J. R., & Hoskin, D. W. (2017). [10]-Gingerol, a major phenolic constituent of ginger root, induces cell cycle arrest and apoptosis in triple-negative breast cancer cells. *Experimental and Molecular Pathology*, *102*(2), 370–376. http://dx.doi.org/10.1016/j.yexmp.2017.03.006

Dandawate P.R., Subramaniam D., Padhye S.B., Anant S. (2016) Bitter melon: A panacea for inflammation and cancer. Chin. *J. Nat. Med*. (14),81–100. doi: 10.1016/S1875-5364(16)60002-X.

Das, M., Kandimalla, R., Gogoi, B., Dutta, K. N., Choudhury, P., Devi, R., Dutta, P. P., Talukdar, N. C., & Samanta, S. K. (2019). Mahanine, A dietary phytochemical, represses mammary tumor burden in rat and inhibits subtype regardless breast cancer progression through suppressing self-renewal of breast cancer stem cells. *Pharmacological Research*, *146*. https://doi.org/10.1016/j.phrs.2019.104330

Durgawale, P. P., & Datkhile, K. D. (2016). Study of in-vitro anti-cancer and anti-oxidative properties of methanolic extract of *Punica granatum* flowers. *Der Pharmacia Lettre*, *8*(11), 197–201.

Elgndi, M. A., Filip, S., Pavlić, B., Vladić, J., Stanojković, T., Žižak, Ž., & Zeković, Z. (2017). Antioxidative and cytotoxic activity of essential oils and extracts of Satureja montana L., Coriandrum sativum L. and Ocimum basilicum L. obtained by supercritical fluid extraction. The Journal of Supercritical Fluids, 128, 128–137.https://doi.org/10.1016/j.supflu.2017.05.025

Guneidy, R. A., Zaki, E. R., Gad, A. A. M., Saleh, N. S. E.-D., & Shokeer, A. (2022). Evaluation of phenolic content diversity along with antioxidant/pro-Oxidant, 64 glutathione transferase inhibition, and cytotoxic potential of selected commonly used plants. Preventive Nutrition and Food Science, 27(3), 282–298. https://doi.org/10.3746/pnf.2022.27.3.282

Iqbal, J., Abbasi, B. A., Mahmood, T., Kanwal, S., Ali, B., Shah, S. A., & Khalil, A. T. (2017). Plant-derived anticancer agents: A green anticancer approach. In *Asian Pacific Journal of Tropical Biomedicine*, *7*(12), 1129–1150. https://doi.org/10.1016/j.apjtb.2017.10.016

Kikuchi, H., Yuan, B., Hu, X., & Okazaki, M. (2019). Chemopreventive and anticancer activity of flavonoids and its possibility for clinical use by combining with conventional chemotherapeutic agents. *Am J Cancer Res*, *9*(8).

Kilcar, A. Y., Yildiz, O., Dogan, T., Sulu, E., Takan, G., & Muftuler, F. Z. B. (2020). The effect of bitter melon (Momordica charantia) extract on the uptake of 99mTc labeled paclitaxel: In vitro monitoring in breast cancer cells. *Anti-Cancer Agents in Medicinal Chemistry*, 20(12), 1497–1503. https://doi.org/10.2174/1871520620666200424124746

Lucci, P., Pacetti, D., Loizzo, M. R., & Frega, N. G. (2015). Punica granatum cv. Dente di Cavallo seed ethanolic extract: Antioxidant and antiproliferative activities. *Food Chemistry*, *167*, 475–483. http://dx.doi.org/10.1016/j.foodchem.2014.06.123

Luna-Guevara, Ma. L., Luna-Guevara, J. J., Hernández-Carranza, P., Ruíz-Espinosa, H., & Ochoa-Velasco, C. E. (2018). Chapter 3 - phenolic compounds: A good choice against chronic degenerative diseases (59),79–108. https://doi.org/10.1016/B978-0-444-64179-3.00003-7

Mainasara, M. M., Abu Bakar, M. F., & Linatoc, A. C. (2018). Malaysian medicinal plants' potential for breast cancer therapy. *Asian Journal of Pharmaceutical and Clinical Research*, *11*(6), 101–117. https://doi.org/10.22159/ajpcr.2018.v11i6.24322

Mandal, A., Bishayee, A., & Lam, C. W. K. (2015). Mechanism of breast cancer preventive action of pomegranate: Disruption of estrogen receptor and Wnt/β-catenin signaling pathways. *Molecules*, *20*(12), 22315–22328. https://doi.org/10.3390/molecules201219853\

Meysami, M., Rahaie, M., Ebrahimi, A., & Samiee, F. (2021). Four Matrix Metalloproteinase genes involved in murine breast cancer affected by ginger extract. *Gene Reports*, 25, 101332. https://doi.org/10.1016/j.genrep.2021.101332

Moga, M. A., Dimienescu, O. G., Bălan, A., Dima, L., Toma, S. I., Bîgiu, N. F., & Blidaru, A. (2021). Pharmacological and therapeutic properties of *Punica granatum* phytochemicals: possible roles in breast cancer. *Molecules*, *26*(4), 1054. https://doi.org/10.3390/molecules26041054

Mónica, G. C., Marcela, M. C. G., Astolfo, C. Z. C., & Ricardo, V. B. (2020). Antiproliferative activity of total extracts from *Annona squamosa, Petiveria alliacea* and *Punica granatum* on cancer cell lines. *Pharmacologyonline*, *3*, 7–18.

Nadaf, S., Desai, R., More, T., Shinde, P., Dakare, S., & Killedar, S. (2020). Antiproliferative and caspase-mediated apoptosis inducing effects of *Murraya koenigii* seeds against cancer cells. *South African Journal of Botany*, *132*, 328–337. https://doi.org/10.1016/j.sajb.2020.05.021

Patel, S. K., Shutter, A. K., Patil, R., Desangi, A., Malali, V., Patil, J., Patil, S., Das, K. K., & Parvatikar, P. P. (2022). In-vitro antioxidant, anti-Inflammatory and cytotoxic effects of different solvent extraction Terminalia chebula, Terminalia billerica, Phyllanthus emblica. Research Journal of Pharmacy and Technology, 15(7), 2940–2944. https://doi.org/10.52711/0974-360X.2022.00490

Sai Saraswathi, V., Rajaguru, P., & Santhakumar, K. (2017). Solar catalysed activity against methyl orange dye, cytotoxicity activity of MCF-7 cells lines and identification of marker compound by HPTLC of Lagerstroemia speciosa. Journal of Photochemistry and Photobiology B: Biology, 170, 263–270. http://dx.doi.org/10.1016/j.jphotobiol.2017.04.015

Sai Saraswathi, V., Saravanan, D., & Santhakumar, K. (2017). Isolation of quercetin from the methanolic extract of Lagerstroemia speciosa by HPLC technique, its cytotoxicity against MCF-7 cells and photocatalytic activity. Journal of Photochemistry and Photobiology B: Biology, 171, 20–26. https://doi.org/10.1016/j.jphotobiol.2017.04.031

S.K. Samanta, A. Sehrawat, S.H. Kim, E.R. Hahm, Y. Shuai, R. Roy, et al. (2016) Disease subtype-independent biomarkers of breast cancer chemoprevention by the ayurvedic medicine phytochemical. *Withaferin A, J. Natl. Cancer Inst. 109*, 1–13.

S.K. Samanta, R. Kandimalla, B. Gogoi, K.N. Dutta, P. Choudhury, P.K. Deb, (2018) Phytochemical portfolio and anticancer activity of *Murraya koenigii* and its primary active component, *Mahanine. Pharmacol. Res. 129*,227–236.

Sreeja, S.; Santhosh Kumar, T.R.; Lakshmi, B.S.; Sreeja, S. (2012) Pomegranate extract demonstrate a selective estrogen receptor modulator profile in human tumor cell lines and *in vivo* models of estrogen deprivation. *J. Nutr. Biochem*. ,*23*, 725–732.

Sur, S., & Ray, R. B. (2020). Bitter Melon (*Momordica charantia*), a nutraceutical approach for cancer prevention and therapy. *Cancers, 12*(8), 2064. https://doi.org/10.3390/cancers12082064

Talib, W. H. (2017). Consumption of garlic and lemon aqueous extracts combination reduces tumor burden by angiogenesis inhibition, apoptosis induction, and immune system modulation. Nutrition, 43–44, 89–97. http://dx.doi.org/10.1016/j.nut.2017.06.015

Tricco, A. C., Lillie, E., Zarin, W., O'Brien, K. K., Colquhoun, H., Levac, D., Moher, D., Peters, M. D. J., Horsley, T., Weeks, L., Hempel, S., Akl, E. A., Chang, C., McGowan, J., Stewart, L., Hartling, L, Aldcroft, A., Wilson, M. G., Garritty, C., Lewin, S., Godfrey, C. M., Macdonald, M. T., Langlois, E. V., Soares-Weiser, K., Moriarty, J., Clifford, T., Tunçalp, Ö., & Straus, S. E. (2018). PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Annals of Internal Medicine., 169(7):467-473.* https://doi.org/10.7326/M18-0850

Wan Yusof, W. N. S., & Abdullah, H. (2020). Phytochemicals and cytotoxicity of Quercus infectoria ethyl acetate extracts on human cancer cells. Tropical Life Sciences Research, 31(1), 69–84. https://doi.org/10.21315/tlsr2020.31.1.5

World Health Organization. (2020). *Breast cancer*. World Health Organization. https://www.who.int/news-room/fact-sheets/detail/breast-cancer

Yang, Q.Q., Cheng, L.-Z., Zhang, T., Yaron, S., Jiang, H.-X., Sui, Z.-Q., & Corke, H. (2020). Phenolic profiles, antioxidant, and antiproliferative activities of turmeric (*Curcuma longa*). *Industrial Crops and Products*, *152*, 112561. https://doi.org/10.1016/j.indcrop.2020.112561

Younas, M., Hano, C., Giglioli-Guivarc'H, N., & Abbasi, B. H. (2018). Mechanistic evaluation of phytochemicals in breast cancer remedy: Current understanding and future perspectives. *RSC Advances*, *8*(52), 29714–29744. https://doi.org/10.1039/c8ra04879g

Zakaria. M, (2010). *Traditional Malay medicinal plants*. ITBM.

Zheng, X.-H., Yang, J., Lv, J.-J., Zhu, H.-T., Wang, D., Xu, M., Yang, C.-R., & Zhang, Y.-J. (2018). Phyllaciduloids A–D: Four new cleistanthane diterpenoids from Phyllanthus acidus (L.) Skeels. Fitoterapia, 125, 89–93. https://doi.org/10.1016/j.fitote.2017.12.005