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Review Article

Cytotoxic effects of plants used in the treatment of breast cancer: A systematic review

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Abstract: Breast cancer is a multifactorial disorder with a major impact on populations worldwide. Because approved medicines such as tamoxifen, fulvestrant, and doxorubicin can produce adverse effects, medicinal plants continue to be investigated as alternative sources of breast-cancer treatments. This systematic review examined articles published from 2015 to 2021 and retrieved through PubMed, ScienceDirect, and Google Scholar. The review identified and reorganized evidence on the cytotoxic potency of plant extracts and compounds tested against MCF-7 and T47D breast-cancer cell lines. Extracts were classified as having high, moderate, or low activity according to their half-maximal inhibitory concentration (IC_{50}), with tamoxifen used as a reference treatment. The highest activity against MCF-7 cells was reported for the methanolic leaf extract of *Sideroxylon oxyacanthum* (Sapotaceae; $IC_{50} = 0.09 \pm 0.02\,\mu g/mL$). Asteraceae was the most frequently represented plant family. For T47D cells, the highest activity was reported for Fraction A of the ethyl-acetate leaf fraction of *Ficus septica* Burm. (Moraceae; $IC_{50} = 2.57\,\mu g/mL$). The evidence most frequently concerned Sapotaceae, Flacourtiaceae, Ranunculaceae, Verbenaceae, Lamiaceae, Asteraceae, and Moraceae, whereas fewer data were available for Convolvulaceae, Thymelaeaceae, and Orchidaceae. Further controlled studies are required to validate promising plant-derived cytotoxic candidates and determine their selectivity and mechanisms of action.

Keywords: breast cancer; cytotoxicity; MCF-7 cells; medicinal plants; plant extracts; T47D cells.

1. Introduction

Cancer is a complex global health problem that affects people of all ages and remains the second leading cause of death worldwide, accounting for approximately one in six deaths (The global challenge of cancer, 2020). GLOBOCAN 2020 identified breast cancer as one of the most frequently diagnosed cancers and the fifth leading cause of cancer-related mortality, with an estimated 2.3 million new cases globally (Łukasiewicz et al., 2021). Breast-cancer mortality remains substantial despite continued improvements in detection and treatment.

The long-term financial burden of breast cancer is also considerable. Approximately one in eight women will develop invasive breast cancer during her lifetime, and the associated treatment costs can persist for years after diagnosis. In the United States, annual medical expenditure for breast cancer was projected to reach US$16.5 billion in 2020, exceeding expenditure for several other major cancers (Seegert, 2020).

Breast-cancer management includes hormonal therapy, chemotherapy, surgery, radiotherapy, and targeted therapy. Tamoxifen is approved for adjuvant hormonal treatment of estrogen-receptor-positive early-stage breast cancer, while aromatase inhibitors such as anastrozole, letrozole, and exemestane are used in postmenopausal women (Hormone Therapy for Breast Cancer Fact Sheet, 2021). Five or more years of adjuvant tamoxifen after surgery reduces recurrence, contralateral breast cancer, and long-term mortality (Davies et al., 2011).

Many cancer treatments rely on cytotoxic agents that damage both malignant and healthy cells and can therefore produce substantial adverse effects during and after therapy (Laskar, Lourembam and Mazumder, 2020). The heterogeneous genetic and molecular pathways involved in breast cancer also produce variable clinical responses and complicate treatment selection (Hennessy et al., 2009; Caffarel et al., 2016). These limitations have encouraged research into plant-derived compounds that may selectively target cancer cells.

The National Cancer Institute has screened approximately 35,000 plant species for potential anticancer activity, of which about 3,000 demonstrated reproducible activity (Desai et al., 2008). Plant secondary metabolites include alkaloids, terpenoids, tannins, pigments, flavonoids, and other polyphenols. Several of these compounds exhibit antioxidant, apoptosis-inducing, and anticancer properties and may alter methylation, acetylation, phosphorylation, and other pathways associated with cancer development (Greenwell and Rahman, 2015).

The MTT assay is widely used to determine the cytotoxic activity of plant extracts and compounds. Metabolically active cells reduce yellow 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide to insoluble purple formazan. After solubilization, absorbance is measured at approximately 500–600 nm; greater colour intensity indicates a larger number of viable cells (MTT Assay Protocol for Cell Viability and Proliferation, 2021).

This systematic review evaluated the cytotoxic activity

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of plant extracts and isolated compounds against the MCF-7 and T47D breast-cancer cell lines and categorized the evidence according to reported IC$_{50}$ values.

2. Methods

2.1. Search Strategy

The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance (Moher et al., 2009). PubMed, ScienceDirect, and Google Scholar were searched for articles published between 2015 and 2021. Search terms included "breast cancer", "MTT assay", "MCF-7", "T47D", "plant treatment", "IC$_{50}$ values", "cytotoxicity", "cytotoxic", "cell lines", and "herbal plants".

2.2. Eligibility Criteria

Studies were included when they were peer-reviewed original research articles written in English, reported sufficient methodological information, evaluated a plant extract or compound using the MTT assay, and provided IC$_{50}$ values for MCF-7 or T47D breast-cancer cells. In-vivo studies, reviews and other non-laboratory studies, non-English articles, and studies that did not report IC$_{50}$ values were excluded.

2.3. Study Selection and Data Extraction

The database searches identified 228 records: 120 concerning MCF-7 cells and 108 concerning T47D cells. Restriction to the publication period removed 61 records. Screening of the remaining 167 records by organism type excluded 10 articles. Full texts of 157 articles were assessed against the eligibility criteria, and 115 were excluded. Forty-two studies were included in the final review (Figure 1).

For each eligible study, the plant species, family, plant part, extract or isolated compound, breast-cancer cell line, IC$_{50}$ value, and reference were recorded. Extracts with IC$_{50}$ $< 4\,\mu$g/mL were categorized as highly cytotoxic, values from 4 to 400 μg/mL as moderately cytotoxic, and values above 400 μg/mL as having low cytotoxicity.

3. Results

Six plant extracts exhibited high cytotoxicity against MCF-7 cells (Table 1), while the two fractions of *Ficus septica* were the only extracts categorized as highly active against T47D cells (Table 2). Most reported extracts showed moderate activity (Tables 3 and 4), and a smaller group showed low activity (Tables 5 and 6).

The strongest MCF-7 response was reported for the methanolic leaf extract of *Sideroxylon oxyacanthum* (IC$_{50}$ $= 0.09\,\mu$g/mL). Methanolic extracts of *Dovyalis abyssinica* stem bark and the whole aerial part of *Clematis simensis* produced IC$_{50}$ values of 0.21 and 0.24 μg/mL, respectively (Tuasha et al., 2019). Other highly active MCF-7 extracts were obtained from *Vitex trifolia*, *Clerodendrum myricoides*, and *Vernonia leopoldi*.

For T47D cells, Fraction A and Fraction B derived from the ethyl-acetate leaf fraction of *Ficus septica* produced IC$_{50}$ values of 2.57 and 2.73 μg/mL, respectively (Nugroho et al., 2015).

Table 1: Plant extracts with high cytotoxicity against MCF-7 breast-cancer cells.

Plant species	Family	Plant part	Extract/compound	IC$_{50}$ (μg/mL)	Reference
Sideroxylon oxyacanthum	Sapotaceae	Leaves	Methanol	0.09	Tuasha et al., 2019
Dovyalis abyssinica	Flacourbitaceae	stem bark	Methanol	0.21	Tuasha et al., 2019
Clematis simensis	Ranunculaceae	whole aerial part	Methanol	0.24	Tuasha et al., 2019
Vitex trifolia	Verbenaceae	Leaves	Petroleum ether	0.41	Garbi, Osman and Kabbashi, 2015
Clerodendrum myricoides	Lamiaceae	Leaves	Methanol	0.74	Tuasha et al., 2019
Vernonia leoplodi	Asteraceae	Leaves	Ethyl acetate	3.5	Tuasha et al., 2019

Table 2: Plant extracts with high cytotoxicity against T47D breast-cancer cells.

Plant species	Family	Plant part	Extract/compound	IC$_{50}$ (μg/mL)	Reference
Ficus septica	Moraceae	Leaves	Fraction A	2.57	Nugroho et al., 2015
Ficus septica	Moraceae	Leaves	Fraction B	2.73	Nugroho et al., 2015

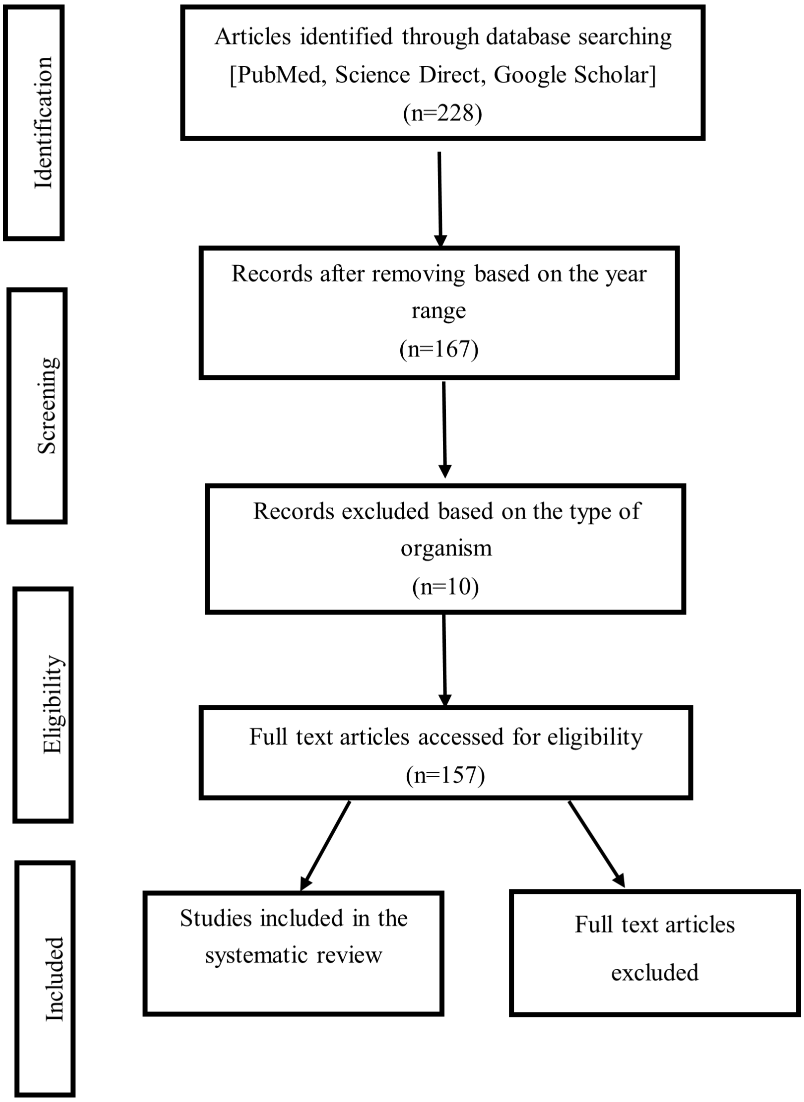

Figure 1: PRISMA flow diagram for identification, screening, eligibility assessment, and inclusion of studies.

Table 3: Plant extracts with moderate cytotoxicity against MCF-7 breast-cancer cells.

Plant species	Family	Plant part	Extract/compound	IC$_{50}$ (μg/mL)	Reference
Annona muricata	Annonaceae	Fruit	IL-GFE	4.75	Daddiouaissa et al., 2019
Curcuma zanthorrhiza	Zingiberaceae	Rhizome	Ethanol	6.13	Haryanti, Ratnawati and Rahmawati, 2020
Vitex trifolia	Verbenaceae	Leaves	Methanol	6.72	Garbi, Osman and Kabbashi, 2015
Achillea millefolium	Asteraceae	Flower	Ethanol	7.3	Amini Navaie et al., 2016
Terminalia bellerica	Combretaceae	Stem bark	Ethanol	9	Diab et al., 2015
Baeckea frutescens	Myrtaceae	Leaves	Hexane	10	Shahruzaman et al., 2019a
Achillea millefolium	Asteraceae	Flower	Ethanol	11.7	Amini Navaie et al., 2016
Tribulus terrestris	Zygophyllaceae	Seed	Methanol	12.19	Patel et al., 2019
Dendrophthoe pentandra	Loranthaceae	Leaves	Ethyl acetate	14.42	Nik Zainuddin and Sul'ain, 2015
Achillea millefolium	Asteraceae	Flower	Methanol	14.6	Amini Navaie et al., 2016
Bauhinia rufescens	Leguminosae	Leaves	Methanol	14.75	Garbi, Osman, & Kabbashi, 2015
Dendrophthoe pentandra	Loranthaceae	Leaves	Methanol	17.7	Nik Zainuddin and Sul'ain, 2015
Anogeissus latifolia	Combretaceae	Stem and leaves	Ethanol	20.1	Diab et al., 2015
Eupatorium cannabinum	Asteraceae	Aerial	Chloroform	21.39	Abuali et al., 2021
Baeckea frutescens	Myrtaceae	Leaves	Hexane	22	Shahruzaman et al., 2019a
Ferula gotrifida	Apiaceae	Aerial part	F. gotrifida essential oil	22	Tavakoli et al., 2017
Acacia catechu	Leguminosae	Fruit	Ethanol	22.8	Diab et al., 2015
Bauhinia rufescens	Leguminosae	Leaves	Petroleum ether	23.77	Garbi, Osman, and Kabbashi, 2015

Continued on next page

Table 3 continued

Plant species	**Family**	**Plant part**	**Extract/compound**	**IC$_{50}$ (μg/mL)**	**Reference**
Moringa oleifera	Moringaceae	Leaves	Ethanol	26.4	Diab et al., 2015
Tribulus terrestris	Zygophyllaceae	Leaves	Saponin	28.32	Patel et al.,2019
Artocarpus heterophyllus	Moraceae	Heartwoods	Artocarpin	28.73	Daud et al., 2019
Achillea millefolium	Asteraceae	Leaves	Ethanol	37.46	Amini Navaie et al., 2016
Achillea millefolium	Asteraceae	Leaves	Methanol	40.54	Amini Navaie et al., 2016
Solanum nigrum L.	Solanaceae	Fruit	Ethanol	40.77	Churiyah, Ningsih and Firdayani, 2020
Tribulus terrestris	Zygophyllaceae	Seed	Saponin	41.23	Patel et al.,2019
Albizia zygia	Leguminosae	Root	Petroleum ether	41.5	Appiah-Opong et al., 2016
Artocarpus heterophyllus	Moraceae	Heartwoods	Cycloartocarpin	43.31	Daud et al., 2019
Achillea millefolium	Asteraceae	Leaves	Ethanol	47.05	Amini Navaie et al., 2016
Sideroxylon oxyacanthum	Sapotaceae	Leaves	Aqueous	49	Tuasha et al., 2019
Baeckea frutescens	Myrtaceae	Branch	Ethanol 70%	53	Shahruzaman et al., 2019b
Achillea millefolium	Asteraceae	Leaves	Methanol	54.91	Amini Navaie et al., 2016
Ardisia crispa	Myrsinaceae	Leaves	Ethyl acetate	54.98	Nordin et al., 2018
Cotinus coggygria	Anacardiaceae	Leaves	Aqueous Ethanol	55	Gospodinova et al., 2017
Ardisia crispa	Myrsinaceae	Leaves	Hydro methanol	57.35	Nordin et al., 2018
Cinnamomum zeylanicum	Lauraceae	Bark	Methanol	58	Wahab and Adzmi, 2017
Eupatorium cannabinum	Asteraceae	Aerial	n-hexane	60.23	Abuali et al., 2021
Artocarpus heterophyllus	Moraceae	Heartwoods	Cyanomaclurin	71.31	Daud et al., 2019
Bellis perennis	Asteraceae	Flower	Methanol	71.6	Karakas et al., 2015
Hyptis pectinata	Lamiaceae	Leaves	Hyptolide	76.76	Suzery, Cahyono and Amalina, 2020
Artocarpus heterophyllus	Moraceae	Heartwoods	Artocarponanone	77.28	Septama and Nik Mat Daud, 2021
Thymus linearis	Lamiaceae	Whole plant	T. linearis essential oil	79.55	Bashir et al., 2019
Achillea millefolium	Asteraceae	Flower	Aqueous	79.80	Amini Navaie et al., 2016
Eupatorium cannabinum	Asteraceae	Aerial	Methanol	81.74	Abuali et al., 2021
Dendrophthoe pentandra	Loranthaceae	Leaves	Chloroform	82.33	Nik Zainuddin and Sul'ain, 2015
Tribulus terrestris	Zygophyllaceae	Leaves	Methanol	89.78	Patel et al.,2019
Achillea millefolium	Asteraceae	Flower	Aqueous	92.04	Amini Navaie et al., 2016
Albizia zygia	Leguminosae	Root	Ethyl acetate	92.2	Appiah-Opong et al., 2016
Achillea millefolium	Asteraceae	Leaves	Aqueous	97.47	Amini Navaie et al., 2016
Origanum dayi	Lamiaceae	Aerial	Ethanol	99	Yousef et al., 2018
Albizia zygia	Leguminosae	Root	Dichloromethane	>100	Appiah-Opong et al., 2016
Dendrophthoe pentandra	Loranthaceae	Leaves	Diethyl ether	101.57	Nik Zainuddin and Sul'ain, 2015
Carthamus tinctorius L	Asteraceae	Flower and leaves	Safflower Polysaccharide	120	Luo et al., 2015
Nendran Banana	Musaceae	Peel	Methanol	120.6	Durgadevi, Saravanan and Uma, 2019
Chrysanthemum coronarium L.	Asteraceae	Aerial	Methanol	138.5	Abu-rish et al., 2016
Cinnamomum zeylanicum	Lauraceae	Bark	Methanol	140	Wahab and Adzmi, 2017
Achillea millefolium	Asteraceae	Leaves	Aqueous	147.49	Amini Navaie et al., 2016
Bellis perennis	Asteraceae	Flower	Water	147.6	Karakas et al., 2015
Curcuma longa Linn	Zingiberaceae	Rhizome	Distilled water	163.19	Sadashiva, Hussain and Nanjundaiah, 2019
Convolvulus galaticus	Convolvulaceae	Aerial	Dichloromethane	172.4	Karakas et al., 2015
Ipomoea aquatica	Convolvulaceae	Whole plant	Water fraction	173.1	Sasikala, Sundaraganapathy and Mohan, 2020
Ipomoea aquatica	Convolvulaceae	Whole plant	Water fraction	182.8	Sasikala, Sundaraganapathy and Mohan, 2020
Clematis simensis	Ranunculaceae	whole aerial part	Chloroform	190	Tuasha et al., 2019
Ipomoea aquatica	Convolvulaceae	Whole plant	Hydroalcohol	220.9	Sasikala, Sundaraganapathy and Mohan, 2020
Sideroxylon oxyacanthum	Sapotaceae	Leaves	Ethyl acetate	240	Tuasha et al., 2019
Ipomoea aquatica	Convolvulaceae	Whole plant	Ethyl acetate	248.6	Sasikala, Sundaraganapathy and Mohan, 2020
Ipomoea aquatica	Convolvulaceae	Whole plant	Ethyl acetate	276.3	Sasikala, Sundaraganapathy and Mohan, 2020
Bellis perennis L.	Asteraceae	Flower	Hexane	>200	Karakas et al., 2015
Bellis perennis L.	Asteraceae	Flower	Dichloromethane	>200	Karakas et al., 2015
Convolvulus galaticus	Convolvulaceae	Aerial	Hexane	>200	Karakas et al., 2015
Trifolium pannonicum Jacq.	Fabaceae	Aerial	Hexane	>200	Karakas et al., 2015
Trifolium pannonicum Jacq.	Fabaceae	Aerial	Dichloromethane	>200	Karakas et al., 2015
Lysimachia vulgaris L.	Primulaceae	Aerial	Hexane	>200	Karakas et al., 2015
Lysimachia vulgaris L.	Primulaceae	Aerial	Dichloromethane	>200	Karakas et al., 2015
Albizia zygia	Leguminosae	Root	Hydroethanol	377.5	Appiah-Opong et al., 2016

Table 4: Plant extracts with moderate cytotoxicity against T47D breast-cancer cells.

Plant species	**Family**	**Plant part**	**Extract/compound**	**IC$_{50}$ (μg/mL)**	**Reference**
Garcinia cowa Roxb.	Clusiaceae	Stem bark	Ethanol	5.10	Husni et al., 2015
Garcinia cowa Roxb.	Clusiaceae	Leaves	Ethanol	6.13	Wahyuni, Triastuti and Arifin, 2015
Green tea	Theaceae	-	EGCG	14.17	Moradzadeh et al., 2017
Green tea	Theaceae	-	EGCG	22.31	Moradzadeh et al., 2017
Moringa oleiferna	Moringaceae	Leaves	Ethanol	33.5	Diab et al., 2015
Acacia catechu	Leguminosae	Fruits	Ethanol	38.5	Diab et al., 2015
Anogeissus latifolia	Combretaceae	Stem and leaves	Ethanol	42.2	Diab et al., 2015
Terminalia bellerica	Combretaceae	Stem bark	Ethanol	43.7	Diab et al., 2015
Green tea	Theaceae	-	EGCG	46.88	Moradzadeh et al., 2017
Zanthoxylum acanthopodium	Rutaceae	Fruits	Ethyl acetate	48.94	Satria et al., 2019
Vernonia amygdalina Del	Asteraceae	Leaves	Ethyl acetate	55.5	Lifiani et al., 2018
Cotinus coggygria Scop.	Anacardiaceae	Leaves	Aqueous Ethanol	61.1	Gospodinova et al., 2017
Litsea cubeba Lour.	Lauraceae	Fruit	Ethanol	63.7	Dalimunthe, Hasibuan and Satria, 2017
Litsea cubeba Lour.	Lauraceae	Fruit	n-hexane	67.52	Dalimunthe, Hasibuan and Satria, 2017
Litsea cubeba Lour.	Lauraceae	Heartwood	Ethyl acetate	71.23	Dalimunthe, Hasibuan and Satria, 2017
Litsea cubeba Lour.	Lauraceae	Fruit	Ethyl acetate	75.59	Dalimunthe, Hasibuan and Satria, 2017
Litsea cubeba Lour.	Lauraceae	Heartwood	n-hexane	76.34	Dalimunthe, Hasibuan and Satria, 2017
Chrysanthemum coronarium L.	Asteraceae	Aerial	Methanol	79.8	Abu-rish et al., 2016
Thymus linearis	Lamiaceae	Whole plant	T. linearis essential oil	86.2	Bashir et al., 2019
Dendrobium lasianthera	Orchidaceae	Stem	Chloroform	117	Nugroho et al., 2016
Arachnis flos-aeris	Orchidaceae	Stem	Chloroform	139	Nugroho et al., 2016
Dendrobium lasianthera	Orchidaceae	Root	Chloroform	140	Nugroho et al., 2016
Litsea cubeba Lour.	Lauraceae	Heartwood	Ethanol	162.58	Dalimunthe, Hasibuan and Satria, 2017
Vernonia amygdalina Del	Asteraceae	Leaves	n-Hexane	164.85	Lifiani et al., 2018
Hyptis pectinata	Lamiaceae	Leaves	Hyptolide	181.55	Suzery, Cahyono and Amalina, 2020
Arachnis flos-aeris	Orchidaceae	Root	Chloroform	186	Nugroho et al., 2016
Ajuga chia	Lamiaceae	Aerial	Ethanol	200	Yousef et al., 2018
Musa balbisiana	-	Banana peel	Pisang Kepok peel	220.37	Wardati, Holil and Syarifah, 2018
Moringa oleifera	Moringaceae	Leaves	Hexane	235.58	Gaffar, Apriani and Herlina, 2019
Origanum dayi	Lamiaceae	Aerial	Ethanol	250	Yousef et al., 2018
Arachnis flos-aeris	Orchidaceae	Leaves	Chloroform	272	Nugroho et al., 2016
Vernonia amygdalina Del	Asteraceae	Leaves	Ethanol	311.72	Lifiani et al., 2018
Arachnis flos-aeris	Orchidaceae	Stem	Water	356	Nugroho et al., 2016
Dendrobium lasianthera	Orchidaceae	Leaves	Chloroform	358	Nugroho et al., 2016
Dendrobium lasianthera	Orchidaceae	Stem	Methanol	390	Nugroho et al., 2016
Dendrobium lasianthera	Orchidaceae	Leaves	Water	396	Nugroho et al., 2016

Table 5: Plant extracts with low cytotoxicity against MCF-7 breast-cancer cells.

Plant species	**Family**	**Plant part**	**Extract/compound**	**IC$_{50}$ (μg/mL)**	**Reference**
Artemisia absinthium	Asteraceae	Whole	Hexane	491.19	Mughees et al., 2018
Ipomoea turpethum	Convolvulaceae	Root	Hexane	516.32	Mughees and Wajid, 2020
Artemisia absinthium	Asteraceae	Root	Hexane	589.15	Mughees et al., 2018
Artemisia absinthium	Asteraceae	Aerial	Hexane	622.1	Mughees et al., 2018
Ipomoea turpethum	Convolvulaceae	Aerial	Hexane	632.01	Mughees and Wajid, 2020
Ipomoea turpethum	Convolvulaceae	Whole	Hexane	650.09	Mughees and Wajid, 2020
Daphne pontica	Thymelaeaceae	Aerial	Petroleum ether	$>$1000	Eskandari et al., 2019
Daphne pontica	Thymelaeaceae	Aerial	Chloroform	$>$1000	Eskandari et al., 2019
Daphne pontica	Thymelaeaceae	Aerial	Ethyl acetate	$>$1000	Eskandari et al., 2019
Daphne pontica	Thymelaeaceae	Aerial	Methanol	$>$1000	Eskandari et al., 2019
Cinnamomum zeylanicum	Lauraceae	Bark	Water	4800	Wahab and Adzmi, 2017
Cinnamomum zeylanicum	Lauraceae	Bark	Water	9000	Wahab and Adzmi, 2017

Table 6: Plant extracts with low cytotoxicity against T47D breast-cancer cells.

Plant species	Family	Plant part	Extract/compound	IC_{50} (μg/mL)	Reference
Arachnis flos-aeris	Orchidaceae	Root	Methanol	457	Nugroho et al., 2016
Dendrobium lasianthera	Orchidaceae	Stem	Water	457	Nugroho et al., 2016
Dendrobium lasianthera	Orchidaceae	Root	Methanol	471	Nugroho et al., 2016
Dendrobium lasianthera	Orchidaceae	Leaves	Methanol	542	Nugroho et al., 2016
Arachnis flos-aeris	Orchidaceae	Stem	Methanol	590	Nugroho et al., 2016
Dendrobium lasianthera	Orchidaceae	Root	Water	628	Nugroho et al., 2016
Arachnis flos-aeris	Orchidaceae	Root	Water	727	Nugroho et al., 2016
Daphne pontica	Thymelaeaceae	Aerial	Petroleum ether	>1000	Eskandari et al., 2019
Daphne pontica	Thymelaeaceae	Aerial	Chloroform	>1000	Eskandari et al., 2019
Daphne pontica	Thymelaeaceae	Aerial	Ethyl acetate	>1000	Eskandari et al., 2019
Daphne pontica	Thymelaeaceae	Aerial	Methanol	>1000	Eskandari et al., 2019
Arachnis flos-aeris	Orchidaceae	Leaves	Methanol	1368	Nugroho et al., 2016
Arachnis flos-aeris	Orchidaceae	Leaves	Water	1436	Nugroho et al., 2016

4. Discussion

This review organized the cytotoxicity evidence into three activity groups. Tamoxifen was used as a clinical reference because it is a potent estrogen antagonist that induces apoptosis in estrogen-receptor-positive cells; a reported IC_{50} of 4.506 μg/mL against MCF-7 cells provides a useful benchmark. Fulvestrant and doxorubicin are also established breast-cancer treatments, although their mechanisms, dosing, and toxicity profiles differ from those of crude plant extracts and isolated natural products.

The six most active MCF-7 extracts represented Sapotaceae, Flacourtiaceae, Ranunculaceae, Verbenaceae, Lamiaceae, and Asteraceae. *Sideroxylon oxyacanthum* was the most potent candidate. Species of *Clematis* contain steroids, macrocyclic compounds, phenolic glycosides, triterpene saponins, coumarins, lignans, volatile oils, and anemonin, which may contribute to their biological activity (Tuasha et al., 2019). The ethyl-acetate leaf fraction of *Vernonia leopoldi* was also highly active, although differences in gene expression among cell lines may affect the observed selectivity.

Asteraceae was the most frequently represented family among extracts with moderate MCF-7 activity. *Achillea millefolium*, *Eupatorium cannabinum*, *Carthamus tinctorius*, *Chrysanthemum coronarium*, and *Bellis perennis* produced a range of responses. For *A. millefolium*, exposure time and extraction solvent influenced IC_{50} values, emphasizing the need to standardize treatment duration and extract composition when comparing studies.

The Combretaceae species *Terminalia bellerica* and *Anogeissus latifolia* showed moderate activity in both cell lines. Their ethanol extracts were more active against MCF-7 than T47D cells, which may reflect differences in cellular origin, morphology, genomes, and susceptibility to chemotherapeutic agents (Diab et al., 2015).

Solanum nigrum contains glycoalkaloids, polyphenols, polysaccharides, and glycoproteins associated with cytotoxic, antioxidant, anti-inflammatory, and anticancer effects. Its ethanolic fruit extract produced moderate MCF-7 cytotoxicity ($IC_{50} = 40.77 \pm 4.86\,\mu$g/mL), consistent with reports that polyphenol-rich extracts can suppress cell-cycle progression and induce apoptosis (Churiyah, Ningsih and Firdayani, 2020).

Within Lamiaceae, hyptolide isolated from *Hyptis pectinata* was more active against MCF-7 cells (76.76 μg/mL) than T47D cells (181.55 μg/mL) (Suzery, Cahyono and Amalina, 2020). Essential oil from *Thymus linearis* showed the same pattern, with IC_{50} values of 79.55 μg/mL for MCF-7 and 86.2 μg/mL for T47D cells (Bashir et al., 2019). Differences in p53 status, estrogen-receptor signalling, protein expression, and essential-oil composition may contribute to these responses.

Baeckea frutescens leaf hexane extract showed time-dependent activity against MCF-7 cells, with IC_{50} values of approximately 22 μg/mL after 48 h and 10 μg/mL after 72 h. Chromatin condensation, membrane blebbing, and increased cell death were more evident after the longer exposure (Shahruzaman et al., 2019a). An ethanolic branch extract also showed moderate activity (Shahruzaman et al., 2019b).

Low activity against MCF-7 cells was reported for hexane extracts of *Ipomoea turpethum* and for petroleum-ether, chloroform, ethyl-acetate, and methanol extracts of *Daphne pontica*. Their high IC_{50} values indicate that these preparations are weak candidates under the tested conditions, although alternative extraction methods or isolated constituents may yield different results.

Only *Ficus septica* displayed high activity against T47D cells. Its Fraction A and Fraction B leaf preparations were both below the 4 μg/mL threshold and therefore represent the most promising T47D candidates identified in the review.

Moderate T47D activity was observed for *Garcinia cowa*, *Zanthoxylum acanthopodium*, *Cotinus coggygria*, *Litsea cubeba*, and several other species. The ethanolic stem-bark extract of *G. cowa* produced an IC_{50} of $5.10 \pm 1.68\,\mu$g/mL and caused morphological changes consistent with cell death (Husni et al., 2015). Extracts of *L. cubeba* heartwood and fruit produced IC_{50} values from 63.7 to 162.58 μg/mL; flavonoids, triterpenoids, steroids, volatile oils, and alkaloids may contribute to this activity (Dalimunthe, Hasibuan and Satria, 2017).

The included studies varied in extraction method, concentration range, exposure duration, cell-culture conditions, and reporting quality. IC_{50} values for crude extracts cannot be interpreted as direct equivalents of clinically administered drugs. Further work should include chemical characterization, testing against non-malignant cells, selectivity indices, mechanism-of-action studies, reproducibility assessments, and in-vivo validation.

5. Conclusion

The families Sapotaceae, Flacourtiaceae, Ranunculaceae, Verbenaceae, Lamiaceae, Asteraceae, and Moraceae contained the most promising candidates for further investigation against MCF-7 and T47D breast-cancer cells. Nevertheless, most evaluated extracts showed moderate or low cytotoxicity. The methanolic leaf extract of *Sideroxylon oxyacanthum* was the most active preparation against MCF-7 cells, while the leaf fractions of *Ficus septica* were the most active against T47D cells.

Future research should prioritize the most active extracts, plant species represented by limited evidence, and standardized comparisons across cell lines. Studies should also evaluate selectivity against normal cells, identify active compounds, establish molecular mechanisms, and assess safety and efficacy in controlled preclinical models before plant-derived candidates are considered for therapeutic development.

Disclosure

The authors report no conflicts of interest.

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