

## PERSPECTIVES AND PHYTOTHERAPEUTIC APPROACHES IN BREAST NEOPLASMS: A SCOPE REVIEW

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*Paloma Horrana Almeida Silva*

<https://lattes.cnpq.br/7287150116566276>

*Morganna Thinesca Almeida Silva*

<http://lattes.cnpq.br/1370186142096453>

*Antonio Francisco de Lima Filho*

<https://lattes.cnpq.br/7287150116566276>

*Jefferson Felipe Calazans Batista*

<http://lattes.cnpq.br/4249834399632505>

*Sonia Oliveira Lima*

<http://lattes.cnpq.br/9026554250991645>

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**Abstract:** Context: Worldwide, breast cancer is the most common cancer in women and also the main cause of death in women, with millions of new cases annually. More individualized and less invasive therapeutic approaches have been developed, such as combined therapy, which uses bioactive phytochemicals from medicinal plants in conjunction with conventional therapies, an important strategy in the fight against breast cancer. Objective: To review the perspectives of the herbal approach to breast neoplasia, analyzing *in vitro* and *in vivo* studies of medicinal plants. Methods: To this end, the model proposed by the PRISMA platform was followed, and bibliographic research was conducted in the Pubmed databases and in the virtual library of the Universidade Tiradentes de Sergipe (UNIT/SE) using eligibility criteria that included articles published in English, addressing the specific topic published in the years 2018 to 2023. Results: Various compounds and plant extracts such as (-)-epicatechin, thymoquinone, curcumin, berberine, palmatine, cannabis sativa, were investigated and considered beneficial for their anti-tumor, anti-proliferative properties and pro-apoptotic, as well as its ability to modulate fundamental cellular processes and control breast cancer tumor progression. Conclusion: There was increasing evidence of the therapeutic potential of natural compounds in the treatment of breast cancer. However, bioavailability and clinical efficacy are still challenges that require future research. **Keywords:** Neoplasia, Breast, Phytotherapy, Scope Review.

## INTRODUCTION

Breast cancer is a public health issue of great relevance, as it is the most common malignancy among women worldwide. In 2020 alone, it was estimated that there were around 2.3 million new cases of the disease, surpassing lung cancer as the most diagnosed neoplasm in women. Even more alarming is the fact that breast cancer tops the list of causes of cancer death in this sex (SUNG, H. et al. 2021).

Characterized by a malignant proliferation of the epithelial cells of the breast ducts or lobules, breast neoplasia is the result of genetic changes, both hereditary and acquired, and presents itself in different forms, whether in the group of invasive carcinomas or *in situ* carcinomas (BOGLIOLO 2021). This results in a highly personalized therapeutic approach, with options determined by the stage of the disease, characteristics of the tumor and the patient's health status (TRAYES, 2021).

Therefore, the main objective of treatment includes: controlling the disease, reducing symptoms and improving the patient's quality of life. But given the organism's rejection rates, toxicity and failure, it has been a growing priority to develop more individualized and less invasive therapeutic approaches, in addition to improving screening methods for early diagnosis (BRAVO et al, 2021).

Thus, within a scenario of searching for better treatments, combined therapy has become an important strategy in the fight against breast cancer, which is mainly due to the high rate of tumor recurrence and the progression of the disease after monotherapeutic treatments, such as surgery, radiotherapy, endocrine therapy and chemotherapy. Thus, one of the innovative options has been the use of bioactive phytochemicals from medicinal plants combined with conventional therapies, using their natural properties to act on the tumor

microenvironment, reducing the resistance of neoplastic cells and the toxicity of treatment (AUMEERUDDY and MAHOMOODALLY, 2019).

It is understood, therefore, that despite increasing advances in alternatives to combat breast cancer, there are still many challenges on the way until this pathology ceases to be an important threat to women's health. This scoping review, therefore, seeks to bring together the perspectives of the phytotherapeutic approach to breast neoplasia, analyzing in vitro and in vivo studies of medicinal plants with positive results in its treatment.

## METHODOLOGY

### THIS IS A SCOPE REVIEW BASED ON THE MODEL PROPOSED BY THE PLATFORM: ``PRISMA``

Articles indexed in Pubmed journals (US National Library of Medicine – NLM) and in the virtual collection of Universidade Tiradentes de Sergipe (UNIT/SE) were used as a database. Descriptors were used: DEC/ MESH as: “*breast neoplasia*”, “*phytotherapy*”, ‘*Chemical Compounds*’ and “*Natural Products*” combined by the Boolean operator AND.

Published articles published in English were included, which addressed the topic “phytotherapeutic perspectives and approaches in breast neoplasms” and published between 2018 and 2023. Articles available only in simple abstracts, duplicates, and of partial relevance to the topic were excluded.

The selection of articles was carried out individually by each researcher involved, strictly following the established eligibility criteria. Subsequently, a consensual analysis of the results was carried out, through reading abstracts and, subsequently, full texts, aiming to reduce the set of articles according to their

level of relevance to the topic.

The initial search was carried out in the aforementioned databases, using the descriptors and eligibility criteria. The identified articles were screened and those that were duplicates or not relevant, according to the exclusion criteria, were eliminated. The abstracts of the remaining studies were read to determine their relevance and suitability to the proposed topic, articles considered relevant were read in full. After complete reading, the articles that fully met the inclusion criteria were selected for analysis and synthesis (table 01).

The data extracted from the included studies were analyzed and synthesized in a descriptive manner, aiming for a clear and objective presentation of the main findings and gaps in the existing literature on phytotherapeutic approaches for the treatment of breast cancer.

## RESULTS AND DISCUSSION

Advances in science have enabled the emergence of more efficient and less invasive treatments for breast cancer. Rautray et al. (2018), explored the anticancer properties of *Adiantum capillus veneris* (ACV) and *Pteris Quadriureta* (PQ) in breast cancer cell lines, demonstrating anti-proliferative properties and induction of apoptosis, with significant interactions of bioactive compounds in cellular processes.

Baraya et al., (2018) demonstrated significant anti-metastatic effects of *Strobilanthes crispus* in in vitro and in vivo models of breast cancer. This natural compound demonstrated the inhibition of migration and invasion of breast cancer cells, associated with the modulation of tumor markers.

Doyle et al. (2018) identified three newchromones in *Dioica* pepper with cytotoxic, estrogenic and antiestrogenic effects, providing a scientific explanation for

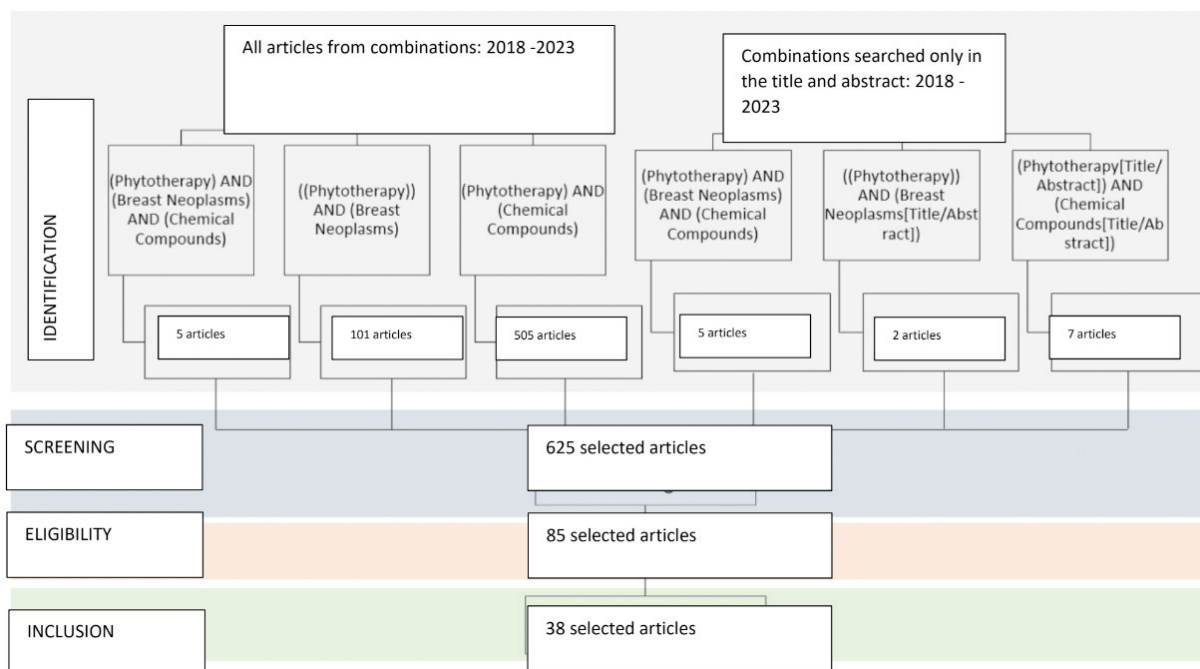


Table 1: identification, screening, eligibility and inclusion of articles on herbal treatment of breast cancer from 2018 to 2023.

Author	Article Title in English	Methodology	Goal	Results	Year of Publication	Plant Species or Plant Secondary Metabolite Used in the Study
<i>Aneta Grabarska et al.</i>	Palmatine, a Bioactive Protoberberine Alkaloid Isolated from <i>Berberis cretica</i> , Inhibits the Growth of Human Estrogen Receptor-Positive Breast Cancer Cells and Acts Synergistically and Additively with Doxorubicin	Experimentos in vitro	To evaluate the effects of palmatine, an alkaloid isolated from <i>Berberis cretica</i> , on breast cancer cells with positive estrogen receptors and its interaction with doxorubicin.	Palmatin inhibited the viability and proliferation of breast cancer cells and acted synergistically and additively with doxorubicin.	2021	<i>Palmatine (alkaloid)</i>
<i>Asma Algebaly et al.</i>	Aqueous Extract of <i>Origanum majorana</i> at Low Temperature (0°C) Promotes Mitochondrial Fusion and Contributes to Induced Apoptosis in Human Breast Cancer Cells	<i>Origanum majorana</i> extract at low temperature (0°C)	To evaluate the effect of <i>Origanum majorana</i> extract on the growth of human breast cancer cells.	<i>Origanum majorana</i> extract decreased the viability of MCF7 cells and induced the expression of apoptotic genes.	2021	<i>Origanum majorana</i>

<i>Brigitta Kis et al.</i>	Cannabidiol—from Plant to Human Body: A Promising Bioactive Molecule with Multi-Target Effects in Cancer	Literature review	Provide an update on the multitarget effects of cannabidiol (CBD) on different types of cancer, focusing on in vitro and in vivo studies, as well as clinical evidence of its anticancer effects.	CBD has been shown to have anti-proliferative, pro-apoptotic, cytotoxic, anti-invasive, anti-angiogenic, anti-inflammatory and immunomodulatory effects in several types of cancer, including breast cancer. It also discusses the pharmacological and toxicological aspects of CBD.	2019	<i>Cannabis sativa (plant)</i>
<i>Carolina Furtado Macruz and Sônia Maria Rolim Rosa Lima</i>	Effects of <i>Cimicifuga racemosa</i> (L.) Nutt on sexual function in women receiving tamoxifen for breast cancer	Prospective study with women treated at the Mastology Outpatient Clinic of the Department of Obstetrics and Gynecology of the Faculty of Medical Sciences of Santa Casa de São Paulo between 2018 and 2021.	To evaluate the effects of <i>Cimicifuga racemosa</i> (L.) Nutt on climacteric symptoms and sexual function in women receiving tamoxifen after breast cancer treatment	The group showed improvements in climacteric symptoms and sexual function after a 6-month follow-up. <i>Cimicifuga racemosa</i> (L.) Nutt promoted improvements in climacteric symptoms and sexual function in women treated surgically for breast cancer.	2022	<i>Cimicifuga racemosa (L.) Nutt</i>
<i>Damilohun Samuel Metibemu et al.</i>	In-silico HMG-CoA reductase-inhibitory and in-vivo anti-lipidaemic/ anticancer effects of carotenoids from <i>Spondias mombin</i>	Characterization of carotenoids from <i>Spondias mombin</i> and in silico HMG-CoA reductase inhibition tests. Treatment of breast cancer model with carotenoid extract.	To investigate the in silico inhibitory effects of HMG-CoA reductase and the in vivo antilipidemic/ anticancer effects of <i>Spondias mombin</i> carotenoids.	Carotenoids from <i>Spondias mombin</i> demonstrated inhibition of HMG-CoA reductase in silico and antilipidemic/anticancer effects in vivo, including reduction of triglycerides, LDL and cholesterol and increase of HDL.	2021	<i>Carotenoids from Spondias mombin</i>
<i>Danielly C. Ferraz da Costa et al.</i>	Bioactive Compounds and Metabolites from Grapes and Red Wine in Breast Cancer Chemoprevention and Therapy	Literature review	To summarize current findings on the molecular mechanisms of bioactive compounds from grapes and red wine and their metabolites with regard to chemoprevention and treatment of breast cancer.	The review highlights flavonoid compounds, such as flavonols, monomeric catechins, proanthocyanidins, anthocyanins, anthocyanidins and non-flavonoid phenolic compounds, such as resveratrol, discussing their structure, metabolism and bioaccessibility. It also includes discussion of in vitro, in vivo studies and clinical trials related to chemoprevention and therapy using these molecules.	2020	<i>Grapes and red wine</i>

<i>Douglas C. Brandao et al.</i>	Arrabidaea chica chloroform extract modulates estrogen and androgen receptors on luminal breast cancer cells	In vitro and in vivo animal model experiments	To evaluate the effects of Arrabidaea chica chloroform extract on breast cancer cells and in an animal model, including the impact on hormone receptors and cell viability.	Chloroform extract from Arrabidaea chica showed antioxidant activity. It was selective for MCF-7 cells, downregulating ESR2 and AR receptors as well as increasing ESR2 expression. Furthermore, the extract had anti-cancer effects in an animal model.	2022	<i>Arrabidaea chica (plant)</i>
<i>Elizabeth Varghese et al.</i>	Anti-Angiogenic Effects of Phytochemicals on miRNA Regulating Breast Cancer Progression	Literature review	Identify miRNAs that regulate tumor angiogenesis and review how selected phytochemicals can modulate miRNA levels to induce anti-angiogenic action in breast cancer.	Phytochemicals such as genistein, epigallocatechin gallate (EGCG) and resveratrol regulate miRNA-21, miRNA-221/222 and miRNA-27, prognostic markers in triple-negative breast cancer (TNBC). Modulation of endothelial cell metabolism.	2020	<i>Genistein, EGCG, resveratrol, cardamomine, curcumin</i>
<i>Almaguer et al.</i>	Anticancer Potential of (-)-epicatechin in a Triple-Negative Mammary Gland Model	Assessment of EC and pathways involved in a TNBC model	Analyze the potential tumor growth inhibition effects of (-)-epicatechin (EC)	EC inhibited tumor growth as efficiently as DOX, modulated signaling pathways and increased the survival of animals treated with EC.	2021	<i>(-) epicatechin</i>
<i>Getinet M. Adinew et al.</i>	Therapeutic Potential of Thymoquinone in Triple-Negative Breast Cancer Prevention and Progression through the Modulation of the Tumor Microenvironment	Review on the role of the tumor microenvironment (TME) in triple-negative breast cancer (TNBC) and the effects of Thymoquinone (TQ) on the TME.	Investigate the potential of TQ in the prevention and treatment of TNBC through modulation of the TME.	TQ exerts anti-metastatic effects independent of its cytotoxic effects.	2021	<i>Thymoquinone (TQ)</i>
<i>Hiva Alipanah et al.</i>	Chitosan nanoparticles containing limonene and limonene-rich essential oils: potential phytotherapy agents for the treatment of melanoma and breast cancers	In vitro experiments	To evaluate the anticancer effects of essential oils from the Citrus family, especially limonene, on melanoma and breast cancer cells, as well as their potential after encapsulation in chitosan nanoparticles.	Chitosan nanoparticles containing Citrus essential oils demonstrated significant anticancer efficacy on melanoma and breast cancer cells in vitro, suggesting their potential as herbal medicine agents.	2021	<i>Citrus and limonene essential oils</i>
<i>Iason Psilopatis et al.</i>	The Role of Bitter Melon in Breast and Gynecological Cancer Prevention and Therapy	Comprehensive literature review on the role of bitter melon in the prevention and therapy of breast and gynecological cancer.	Highlight the promising effects of bitter melon on breast, ovarian and cervical cancer cells.	Promising anticancer effects of bitter melon on breast, ovarian and cervical cancer cells.	2023	<i>Bitter melon (Momordica charantia)</i>

<i>Xu et al.</i>	Anticancer effect of berberine based on experimental animal models of various cancers: a systematic review and meta-analysis	Systematic review and meta-analysis	Investigating the impact of berberine on various types of cancer in healthy animals.	Berberine reduced tumor volume and weight in several cancer types in animal models.	2019	<i>Berberine</i>
<i>Kênia Alves Barcelos et al.</i>	Antitumor Properties of Curcumin in Breast Cancer Based on Preclinical Studies: A Systematic Review	Systematic literature review	To evaluate the antitumor effects of curcumin in breast cancer based on preclinical studies, including assessment of the proliferation, viability and apoptosis of breast cancer cells, as well as tumor volume in animal models.	Curcumin, administered at different concentrations and routes of administration, inhibited proliferation, reduced viability and induced apoptosis in human and animal breast cancer cells. Curcumin nanoparticle formulations, administered orally, via implant and intraperitoneally, reduced tumor volume in human and murine mammary cells in vivo. Nano formulations of curcumin have also had positive effects in inhibiting tumor growth in animal models of breast cancer. Additional randomized clinical trials are needed to evaluate the efficacy and safety of curcumin formulations for clinical use.	2022	<i>Curcumina</i>
<i>M. Zakariyyah Aumeeruddy e M. Fawzi Mahomoodally</i>	Combating Breast Cancer Using Combination Therapy With 3 Phytochemicals: Piperine, Sulforaphane, and Thymoquinone	Literature review	To evaluate the combined effect of three phytochemicals (piperine, sulforaphane and thymoquinone) in combination therapy with conventional chemotherapy for the treatment of breast cancer.	The review highlights the use of combination of phytochemicals as a promising approach for the treatment of breast cancer and emphasizes the importance of nanoformulation of these phytochemicals to improve their bioavailability and therapeutic efficacy.	2019	<i>Piperine, sulforaphane and thymoquinone</i>
<i>Muhammad Imran a, et al</i>	Thymoquinone: A novel strategy to combat cancer: A review	Comprehensive review on the anticancer effects of Thymoquinone (TQ) in various pathways and its use as diet-based therapy.	Highlight the potential of TQ as a pharmacological agent against various types of cancer.	TQ inhibits different stages of cancer, induces apoptosis, regulates pro- and anti-apoptotic genes, reduces metastasis and much more.	2018	<i>Timoquinona (TQ)</i>

<i>Peter Kubatka et al.</i>	Anticancer Activities of <i>Thymus vulgaris</i> L. in Experimental Breast Carcinoma In Vivo and In Vitro	Continuous administration of <i>Thymus vulgaris</i> in the diet of breast cancer models in rats and mice. Histopathological and molecular analysis. In vitro evaluation in MCF-7 and MDA-MB-231 cells.	Evaluate the antitumor effects of <i>Thymus vulgaris</i> L. in experimental mammary carcinoma models.	<i>Thymus vulgaris</i> L. reduced tumor volume in rats and mice, decreased tumor frequency in rats, and exhibited antiproliferative and proapoptotic effects on breast cancer cells in vitro.	2019	<i>Thymus vulgaris</i> L.
<i>Poppy Anjelisa Zaitun Hasibuan et al.</i>	The Anti-Proliferative and Pro-Apoptotic Properties of Ethanol <i>Plectranthus amboinicus</i> (Lour.) Spreng. Leaves Ethanolic Extract Nanoparticles on T47D Cell Lines	Ethanol extraction and nanoparticle preparation	To evaluate the antiproliferative and pro-apoptotic effects of <i>Plectranthus amboinicus</i> extract on T47D breast cancer cells.	The extract inhibited cell proliferation and induced apoptosis.	2019	<i>Plectranthus amboinicus</i>
<i>Doyle et al.</i>	Isolation and identification of three new chromones from the leaves of <i>Dioica</i> pepper with cytotoxic, oestrogenic and anti-oestrogenic effects	Isolation of <i>Dioica</i> pepper compounds	Identify the compounds responsible for the plant's estrogenic effects and investigate the effects on breast and gastric cancer lines.	Quercitrin and three new chromones were identified. One of the compounds had estrogenic and cytotoxic activity, while the other was anti-estrogenic.	2018	<i>Dioica</i> pepper
<i>Satabdi Rautray et al.</i>	Anticancer activity of <i>Adiantum capillus veneris</i> and <i>Pteris quadriureta</i> L. in human breast cancer cell lines	Tests with crude methanolic extract and nanoparticles of <i>Adiantum capillus veneris</i> (ACV) and <i>Pteris Quadriureta</i> (PQ) in breast cancer cell lines MCF7 and BT47.	Evaluate the anticancer activities of ACV and PQ.	Both the crude extract and ACV and PQ nanoparticles showed anti-proliferative and pro-apoptotic properties against MCF7 and BT47 breast cancer cell lines.	2018	<i>Adiantum capillus veneris</i> (ACV) and <i>Pteris Quadriureta</i> (PQ)
<i>Shailima Rampogu et al.</i>	Phytotherapeutic applications of alkaloids in treating breast cancer	Literature review	To evaluate the therapeutic potential of alkaloids in the treatment of breast cancer.	The review highlights 12 alkaloids and their effects on breast cancer, including inducing apoptosis, decreasing tumor volume, inhibiting cell proliferation and migration, and inducing autophagy.	2022	Alkaloids



<i>Sun Xuanrong et al.</i>	Tonkinensina B induces apoptosis through mitochondrial dysfunction and inactivation of the PI3K/AKT pathway in triple-negative breast cancer cells	Cellular cytotoxicity tests and analysis of proteins related to apoptosis in MDA-MB-231 cells treated with Tonkinensin B.	Investigate the effect and mechanism of action of Tonkinensin B in triple-negative breast cancer cells.	Tonkinensin B inhibited the multiplication of MDA-MB-231 cells and induced apoptosis mediated by mitochondrial dysfunction and inhibition of the PI3K/AKT pathway.	2021	<i>Tonkinensina B</i>
<i>Teodora Costea et al.</i>	Alleviation of Multidrug Resistance by Flavonoid and Non-Flavonoid Compounds in Breast, Lung, Colorectal and Prostate Cancer	Literature review	Discuss the influence of plant polyphenols in overcoming multidrug resistance in four types of solid cancer (breast, colon, lung and prostate).	The review highlights the potential of phenolic compounds such as flavones, phenolcarboxylic acids, curcumin, etc. in preventing multidrug resistance in various types of cancer.	2020	<i>Various plant species and phenolic compounds</i>
<i>Vahid F Omrani et al.</i>	Effects of Sambucus ebulus Extract on Cell Proliferation and Viability of Triple-Negative Breast Cancer: An In Vitro and In Vivo Study	Preparation of Sambucus Ebulus extract and tests with triple-negative breast cancer cells (MDAMB-231) and normal breast cells (MCF-10A). Assessment of cell cycle, apoptosis and cell viability. Tumor models in nude mice.	To evaluate the effect of Sambucus Ebulus extract on triple-negative breast cancer cells.	Sambucus Ebulus extract significantly reduced the proliferation and viability of triple-negative breast cancer cells, without toxicity to normal breast cells. Gene expression related to the cell cycle and apoptosis was positively affected by the extract.	2022	<i>Sambucus Ebulus (S. ebulus)</i>
<i>Vandana Singh et al.</i>	Exploration of therapeutic applicability and different signaling mechanism of various phytopharmacological agents for treatment of breast cancer	Literature review	Explore the signaling mechanisms of phytopharmacological agents for the treatment of breast cancer.	The review highlights several treatment strategies and signaling mechanisms, including natural agents such as alkaloids, sesquiterpenes, polyphenols, and flavonoids in medicinal plants and fruits that have potential anticancer activity.	2021	<i>Alkaloids, sesquiterpenes, polyphenols, flavonoids (phytoconstituents)</i>
<i>Venice Wing-Tung Ho et al.</i>	Efficacy and Safety of Chinese Herbal Medicine on Treatment of Breast Cancer: A Meta-analysis of Randomized Controlled Trials	Meta-analysis of randomized controlled trials	To evaluate the clinical efficacy of Chinese herbal medicine in the treatment of breast cancer.	Meta-analysis of 81 randomized clinical trials showed that complementary therapy with Chinese herbal medicine resulted in better tumor responses, increased survival and reduction of tumor markers in breast cancer patients.	2021	<i>Chinese Herbal Medicine</i>

<i>Vida Celeste Rosas-González et al.</i>	Differential effects of alliin and allicin on apoptosis and senescence in luminal A and triple-negative breast cancer: Caspase, DΨm, and pro-apoptotic gene involvement	In vitro experiments	To evaluate the effects of alliin and allicin on cell death, senescence and senolytic potential in luminal A and triple-negative breast cancer cells.	Alliin demonstrated antiproliferative, anticlonogenic and senolytic effects, inducing apoptosis through loss of mitochondrial membrane potential (DΨm) and regulation of pro-apoptotic genes. Alliin, on the other hand, promoted clonogenicity and senescence without inducing apoptosis.	2020	<i>Alliin and allicin</i>
<i>Wala Ben Kridis et al.</i>	Self-medication with herbal medicine and breast cancer survival: a prospective monocentric study	Prospective study with 110 breast cancer patients who were questioned about the use of medicinal herbs.	Determine the impact of herbal autotomy on overall survival.	3-year and 5-year survival rates in patients who did not consume plants versus patients who consumed plants (p = 0.015).	2021	<i>Graviola (39,6%) e Alenda (60,4%)</i>
<i>Xiang Xing et al.</i>	Essential oil extracted from erythrina corallo dendron L. leaves inhibits the proliferation, migration, and invasion of breast cancer cells	In vitro experiments	To evaluate the effects of essential oil extracted from Erythrina corallo dendron leaves on the proliferation, migration and invasion of breast cancer cells.	The essential oil inhibited the proliferation, migration and invasion of breast cancer cells in a dose-dependent manner.	2019	<i>Erythrina corallo dendron (planta)</i>
<i>Yue Li et al.</i>	Ampelopsin Inhibits Breast Cancer Cell Growth through Mitochondrial Apoptosis Pathway	Culture of MDA-MB-231 and MCF-7 breast cancer cells. Assessment of proliferation, apoptosis, mitochondrial membrane potential, ROS and gene expression.	Explore the mechanism of anti-cancer activity of Ampelopsin in breast cancer cells.	Ampelopsin significantly inhibited the proliferation of breast cancer cells and induced apoptosis, associated with mitochondrial damage, increased ROS and regulation of related gene expression.	2021	<i>Ampelopsin</i>
<i>Yusha'u Shu'aibu Baraya, Kah Keng Wong, Nik Soriani Yaacob</i>	Strobilanthes crispus Inhibits Migration, Invasion and Metastasis in Breast Cancer	Use of cell proliferation, wound healing and invasion assays in murine 4T1 and human MDA-MB-231 breast cancer cell lines.	To investigate the potential of S. crispus F3 in preventing metastases in breast cancer.	Significant inhibition of the growth, migration and invasion of breast cancer cells.	2018	<i>F3 de S. crispus</i>

Table 02: Selected Studies on Herbal Medicines in the Treatment of Breast Cancer from 2018 to 2023

their ethnomedicinal use in women's health problems, including breast cancer. These compounds have shown promise in inhibiting the growth of cancer cells and inducing apoptosis.

Imran et al., (2018) and Adinew et al., (2021) studied Thymoquinone, a chemical component of black cumin seed, used in clinical trials for the treatment and prevention of various types of cancer. This substance has the potential to mitigate components of the tumor microenvironment at various stages, through different pathways, being crucial in the prevention and progression of therapy for triple-negative breast cancer.

Xu et al. (2019), in a systematic review and meta-analysis, validated the antitumor effects of berberine in different types of cancer in vivo, including breast cancer. Its antiangiogenic action and its consequences on tumor volume and weight were demonstrated, without significant impacts on the body weight of experimental animals.

Kis et al., (2019) in a literature review, they found that the *Cannabis sativa*, source of cannabidiol (CBD), presents a bioactive molecule with multiple antitumor effects, demonstrating anti-proliferative, pro-apoptotic and immunomodulatory properties in the treatment of cancer, including breast cancer.

Xing et al. (2019) highlight the importance of essential oil: *Erythrina corallodendron L.*, in inhibiting the proliferation, migration and invasion of breast cancer cells, pointing to a possible clinical use of this as a potential adjuvant medicine.

The study by Zaitun Hasibuan et al. (2019) explored the antiproliferative and proapoptotic properties of ethanolic extract nanoparticles of *Plectranthus amboinicus* in T47D breast cancer cell lines, highlighting the importance of technological advances to improve the bioactivity of natural compounds.

Aumeeruddy & Mahomoodally (2019) delved into combined therapies with phytochemicals, such as piperine, sulforaphane and thymoquinone, aiming to reduce the likelihood of resistance development by cancer cells by reducing the therapeutic dose and toxicity. Furthermore, the nanoformulation of these phytochemicals has demonstrated importance in increasing bioavailability, providing a more efficient targeted delivery system.

Kubatka et al. (2019) outlined a study involving *Thymus vulgaris L.*, demonstrating a significant capacity to reduce mammary tumors in in vivo and in vitro models, mainly through the modulation of several molecular markers. The highlighted impacts included the reduction of CD44 and ALDH1A1 expressions and increased Bax expression, indicating a potential regulation of apoptosis and cell proliferation.

Rosas-Gonzalez et al., (2020) showed that compounds such as allicin and alliin, from garlic, have demonstrated differential effects in inducing apoptosis and senescence in different types of breast cancer.

The study by Costea et al. (2020) presents a comprehensive discussion of multidrug resistance in different types of cancer, highlighting the potential role of plant polyphenols in mitigating such resistance. This phenomenon is particularly prominent in solid cancers such as breast, colorectal, lung and prostate, where effective treatments are often hampered by the evolution of cancer cell resistance to different drugs.

Varghese et al. (2020) provide a complementary perspective by exploring the antiangiogenic effects of phytochemicals in regulating breast cancer progression through miRNA modulation. They show that manipulation of miRNA levels by phytochemicals can repress tumor angiogenesis, a critical process for cancer

progression. This approach, when used in conjunction with agents such as Ampelopsin, could represent a promising therapeutic strategy against multidrug resistance.

Ferraz da Costa et al., (2020), focus on the use of phytochemicals as potential chemotherapeutic agents, due to their anti-cancer properties. His research showed the potential of bioactive compounds present in grapes and red wines, such as flavonoids and resveratrol, which have chemopreventive and therapeutic effects in cases of breast cancer.

Li et al. (2021) explored the role of Ampelopsin, a flavonoid, in the treatment of breast cancer, highlighting its ability to inhibit cell growth through the induction of mitochondrial apoptosis. The authors detail how Ampelopsin influences mitochondrial dynamics and the production of reactive oxygen species, pointing out its relevance as an antitumor agent in the context of multidrug resistance, corroborating the findings of Costea et al. (2020).

Almaguer et al. (2021) studied another substance that has also gained prominence, (-)-epicatechin (EC), which demonstrated antiproliferative properties and the potential to increase survival in models of triple-negative breast cancer, one of the most aggressive types of the disease. Its effects modulate important cellular signaling pathways, such as AMPK, Akt and mTOR, and are comparable to those of doxorubicin, a drug widely used to treat this cancer.

Sun et al. (2021) investigated tonkinensin B, isolated from the root of *Sophora tonkinensis* Gagnep, demonstrating antitumor efficacy, specifically in triple-negative breast cancer cells, acting through mitochondrial dysfunction and inactivation of the PI3K/AKT pathway.

Singh et al., (2021) reported that the search for phytopharmacological treatments for breast cancer has revealed the effectiveness

of different phytochemical agents, such as sesquiterpenes, polyphenols, flavonoids and diterpenoids, which show anticancer activity through various signaling pathways.

Alipanah et al. (2021) studied chitosan nanoparticles containing limonene, a major component of citrus essential oils, which showed distinct anticancer efficacies, especially in melanomas and breast cancers.

Algebaly et al. (2021) highlighted the anticancer potential of the aqueous extract of *Origanum majorana*, proving its selective effect against breast cancer cells and its role in promoting apoptosis, essential for the elimination of tumor cells. This plant, rich in flavonoids and phenolics, has the ability to regulate apoptotic genes, being a promising anti-tumor alternative.

Metibemu et al. (2021) investigated carotenoids from *Spondias mombin*, demonstrating in silico inhibitory effects on the HMG-CoA reductase enzyme, associated with antilipemic and anticancer effects in vivo.

Chinese herbal medicine (CHM), as a complement to Western therapy, has demonstrated significant clinical benefits in terms of tumor response and survival. The meta-analysis study by Ho et al. (2021) revealed that patients on additional CHM therapy showed a more pronounced response compared to those on Western therapy alone, supporting the value of integrating alternative therapies.

Grabarska et al., (2021) verified the role of phytotherapeutic applications and alkaloids, such as palmatine, in the treatment of malignant breast neoplasia. Rampogu et al., (2022) also demonstrated that these natural compounds have gained attention due to their therapeutic potential, especially in inducing apoptosis and inhibiting cell proliferation and migration in cases of breast cancer.

Omrani et al. (2022) explored the effects of *Sambucus ebulus* extract, pointing out

a significant reduction in cell proliferation and viability in triple-negative breast cancer, without toxicity to normal breast cells.

Barcelos et al. (2022) addressed the antitumor effects of curcumin, revealing a remarkable inhibition of cell proliferation and induction of apoptosis in breast cancer cell lines. This natural compound has demonstrated, mainly in nanoparticle formulations, effectiveness in reducing tumor volume in animal models. This aspect is relevant when considering potential adjuvant therapies, as it suggests that curcumin may be a promising agent in inhibiting tumor growth.

The chloroform extract of *Arrabidaea chica*, as described by Brandao et al. (2022), has shown modulatory effects on estrogen receptors in luminal breast cancer cells. This hormonal modulation effect is crucial since endocrine therapy is often applied as a therapeutic strategy in hormone-sensitive breast cancers.

Psilopatis et al. (2023) found that Bitter Melon has promising anti-cancer properties for the breast, ovaries and cervix, constituting a recommendation for future research.

The research by Macruz and Lima (2023) focused on the quality of life of patients, demonstrating that the *Cimicifuga racemosa* (L.) Nutt may improve climacteric symptoms and sexual function in women undergoing tamoxifen treatment after breast cancer treatment, thus addressing often overlooked aspects of cancer recovery.

The integration of these research highlights the importance of modulating cellular apoptosis, angiogenesis and resistance to multiple drugs in the treatment of cancer. The use of phytochemicals, such as Ampelopsin, resveratrol and curcumin, appears as a viable alternative to combat resistance to multiple drugs, reinforcing the need for additional research for the clinical validation of these compounds in the oncological context.

Cross-referencing these studies suggests a potential synergy between several strategies to combat multidrug resistance in solid cancers, employing natural compounds to modulate fundamental cellular processes and optimize therapeutic response.

The challenge faced by such natural compounds, however, lies in their bioavailability and clinical efficacy. For example, curcumin has limited bioavailability when taken orally. Likewise, the active components of *Thymus vulgaris* and *Arrabidaea chica* require additional studies to determine their stability, bioavailability and toxicity in clinical contexts.

The prospective study by Ben Kridis et al., (2021), carried out with 110 patients with malignant breast neoplasia, who were asked about the consumption of natural herbs, observed, through the analysis of demographic data, an increase in the risk of death among consumers of Soursop or Alenda, when compared to those who did not consume plants. Therefore, scientific proof of the natural products used by the population as beneficial in the treatment of cancer is essential, avoiding the belief that “if it doesn’t do any good, it doesn’t hurt”.

It appears that these studies, although diverse, converge towards the validation of alternative oncological treatments, using natural compounds, indicating their potential as adjuvant therapies for breast cancer. Continuous research into these substances can, therefore, lead to new therapeutic strategies, overcoming resistance to conventional therapies and improving the management of breast cancer. It is imperative to explore available natural resources in the search for more effective, less invasive and less expensive treatments.

## CONCLUSION

It is concluded that the use of medicinal plants has benefits in the treatment of breast cancer. Therefore, more studies are needed to

confirm these results and better understand the mechanisms of action of these natural compounds in the human body, aiming to optimize integrative therapeutic strategies.

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