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Comprehensive Review on Targeting Breast Cancer through Medicinal Plants

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Abstract: *Breast cancer is a disease characterized by biological heterogeneity, recurrence, metastasis, resistance to treatment, and therapy-associated toxicity. Plants used in medicine contain compounds with different chemical properties that have been studied for their impact on proliferation, apoptosis, cell cycle progression, migration, invasion, angiogenesis, and oncogenic signaling. The purpose of this review is to critically analyze five medicinal plants (Curcuma longa, Withania somnifera, Camellia sinensis, Azadirachta indica, and Catharanthus roseus) with special focus on major constituents, breast cancer models, mechanisms of action, translational data, and limitations. Curcuminoids, withaferin A, epigallocatechin-3-gallate (EGCG), nimbolide, and vinca alkaloids are distinct classes of compounds with considerable amount of experimental data. Nevertheless, the level of evidence varies greatly, as a large number of studies involve pure compounds at concentrations which cannot be easily achieved in humans, and also due to differences in composition, plant part, extraction procedure, and standardization of plant extracts. Clinical evidence is much less extensive than cell line and animal evidence for most of the candidates. Vinca alkaloids represent a unique case as these compounds obtained from the plants are already established anticancer agents, but this does not imply that crude C.roseus preparations can be used in breast cancer. [1–3, 7, 11, 17, 19, 26–29]*

Keywords: Medicinal plants for breast cancer ,phytochemicals: curcumin, withaferin A,epigallocatechin-3-gallate, nimbolide, vincristine, vinblastine. MCF-7,MDA-MB-231,Apoptosis, cell cycle arrest

I. INTRODUCTION

Breast cancer is a group of molecularly and clinically diverse diseases rather than one disease entity. Treatment depends on the hormonal receptor status, HER2 status, stage, grade, molecular features and individual patient factors. Although significant progress has been made in surgery, radiotherapy, endocrine therapy, chemotherapy, HER2 targeted therapy and immunotherapy, resistance to treatment, metastases and side effects are still unmet medical challenges .The contribution of natural products to modern pharmacology is remarkable, and natural products serve as an important source of molecular scaffolds for drug discovery programs. Natural molecules can affect various cellular processes including oxidative stress, inflammation, apoptosis, cell cycle, angiogenesis and epithelial-mesenchymal transition. However, it should be understood that the cytotoxic effect observed in cancer cell cultures cannot be regarded as the proof of efficacy. Crude plant extract, isolated compound and FDA-approved plant-based drug are different levels of pharmacological evidence. This review will consider five medicinal plants chosen to show various phytochemical families and the state of translational research. These plants include C. longa (curcuminoids), W. somnifera (withanolides, withaferin A), C. sinensis (EGCG and other catechins), A. indica (nimbolide and limonoids) and C. roseus (vincristine, vinblastine). The idea is to contrast data in experimental setups instead of ranking these plants for breast cancer therapy. [26–29]

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II. LITERATURE IDENTIFICATION AND REVIEW METHODOLOGY

A focused narrative evidence review was conducted to synthesize experimental and translational evidence on the five selected plants and breast cancer. The searches used combinations of terms for breast cancer, medicinal plants, individual plants, important phytochemicals, cytotoxicity, apoptosis, proliferation, migration, invasion and relevant breast cancer cell lines. Important concepts include: ("breast cancer" OR "breast carcinoma") and ("medicinal plant" or herb or phytochemical) and (anticancer OR cytotoxicity OR apoptosis OR proliferation), followed by individual plant searches. Also, reference lists of pertinent reviews and individual studies were searched. Eligible evidence comprised peer-reviewed individual experimental studies, animal studies, observational and clinical studies, systematic reviews and mechanistic reviews relating to the selected plants and their main phytochemical components. Eligible evidence was classified as in vitro/cell line, animal/preclinical, human observational and human clinical evidence. Evidence on individual isolated components was separated from those on whole plants whenever possible. This is an article review and not an exhaustive systematic search, risk of bias score assessment, or quantitative analysis. PRISMA 2020 is a guideline that should be used when conducting systematic reviews: since this article review is not a systematic review, therefore, the PRISMA flow count has not been presented in this article. [24, 26–29]

III. EXPERIMENTAL MODELS FOR BREAST CANCER AND THEIR INTERPRETATIONS

MCF-7 is typically used as an estrogen-receptor-positive model, while MDA-MB-231 acts as an example of a more aggressive triple-negative phenotype. T47D, BT-474 and SK-BR-3 may serve as other options. Positive effect on one cell line cannot be extrapolated to breast cancer overall. Possible outcomes comprise MTT, resazurin or ATP-based viability tests, cloning survival, apoptosis, cell cycle studies, migration or invasion and signaling pathways investigation. Plant extracts can affect colorimetric methods by means of their pigments or redox capacity: blank-extract, vehicle and positive controls as well as orthogonal assays thus help in interpretation of results. The animal models give data about tumor growth and tolerability but are still pre-clinical. Observational human studies establish correlations, but clinical trials are necessary for proving treatment efficiency. [12, 24, 25]

- **Experimental models used in breast cancer research and their interpretation** [1–3, 7–11, 17–21, 26–29].

Plant	Phytochemical constituents	Anti-breast-cancer Data	Mechanism of Action	Translational Development
C. longa	Curcumin: demethoxycurcumin: bisdemethoxycurcumin	In-vitro/animal Data preliminary human trials	NF-κB, PI3K/AKT, STAT3, apoptosis, cell cycle, EMT	Strong preclinical efficacy not yet proven
W. somnifera	Withaferin A: other withanolides	Stronge preclinical mechanistic animal Data	ROS, STAT3, NF-κB, apoptosis, autophagy	Strong preclinical: Lack of human data
C. sinensis	EGCG and catechins	Cellular cell/preclinical: Data /biomarker study on human	PI3K/AKT, apoptosis, cell cycle, epigenetic pathways	Preclinical/prevention-oriented
A. indica	Nimbolide : limonoids	Predominantly preclinical	NF-κB, STAT3, apoptosis, oxidative stress	Preclinical
C. roseus	Vincristine: vinblastine	Strong pharmacological and clinical oncology Data for isolated alkaloids	Tubulin/microtubule, mitotic arrest	Purified drugs already established clinically

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Curcuma longa L.: Curcuminoids [1–6, 12].

Parameter	Information
Scientific name	Curcuma longa L.
Family	Zingiberaceae
Plant part	Rhizomes
Image	
Major phytochemicals	Curcumin, demethoxycurcumin (DMC), bisdemethoxycurcumin (BDMC)
Chemical class	Diarylheptanoids (curcuminoids)
Major constituent	Curcumin
Breast-cancer models studied	Hormone-responsive models such as MCF-7 and triple-negative models such as MDA-MB-231
Experimental models	In vitro cancer-cell studies and animal tumour models
Antiproliferative activity	Preclinical studies report reduced breast-cancer cell proliferation
Apoptosis induction	Associated with activation of programmed cell-death pathways
Molecular pathways investigated	NF-κB, PI3K/AKT, STAT3, p53-associated signaling and Wnt/β-catenin
Research limitations	Effects vary with concentration, exposure duration, formulation and cell model: laboratory findings may not translate to clinical benefit
Clinical evidence	Investigated alongside conventional therapies, but evidence is insufficient to establish it as an effective breast-cancer treatment
Future research scope	Improved formulations, comparative evaluation of curcuminoids, dose optimization, selectivity testing and validation in appropriate models

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Withania somnifera (L.) Dunal: Withanolides [7–10].

Parameter	Information
Scientific name	Withania somnifera (L.) Dunal
Family	Solanaceae
Image	
Major phytochemicals	Withaferin A and other withanolides
Chemical class	Steroidal lactones (withanolides)
Major constituent	Withaferin A
Breast-cancer models studied	Breast-cancer cell models including MCF-7 and MDA-MB-231, as described in the review's comparative evidence
Experimental models	Mechanistic studies and animal/preclinical models
Antiproliferative activity	Extensive preclinical literature investigates effects on breast-cancer cell growth
Apoptosis induction	Apoptosis and related cell-death processes have been investigated
Molecular pathways investigated	ROS/redox responses, STAT3, NF-κB, cytoskeletal function and autophagy
Research limitations	Evidence for isolated withaferin A is not equivalent to crude extracts: human evidence is insufficient
Clinical evidence	Insufficient evidence to establish Withania or withaferin A as a breast-cancer treatment

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Future research scope	Standardized extracts/isolated compounds, dose and exposure studies, selectivity testing and translational validation

Camellia sinensis (L.) Kuntze: EGCG [11–16, 22–23].

Parameter	Information
Scientific name	Camellia sinensis (L.) Kuntze
Family	Theaceae
Plant source	Green tea
Image	
Major phytochemicals	EGCG, epigallocatechin, epicatechin and epicatechin gallate
Chemical class	Catechins / polyphenols
Major constituent discussed	Epigallocatechin-3-gallate (EGCG)
Breast-cancer models studied	In vitro models including MCF-7 and MDA-MB-231
Experimental models	Cell-line and animal/preclinical studies: human observational and biomarker/prevention studies
Antiproliferative activity	In vitro studies report effects on proliferation, migration and invasion
Apoptosis induction	Apoptosis and cell-cycle progression have been investigated
Molecular pathways investigated	PI3K/AKT-related signalling, cell-cycle pathways and epigenetic regulation

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Research limitations	Bioavailability, dose, formulation and interactions remain important: human findings do not establish treatment efficacy
Clinical evidence	Human evidence is heterogeneous and includes observational and prevention/biomarker studies: it does not establish treatment of established breast cancer
Future research scope	Clarify relevant exposure, formulation, safety and links between laboratory findings and clinical outcomes

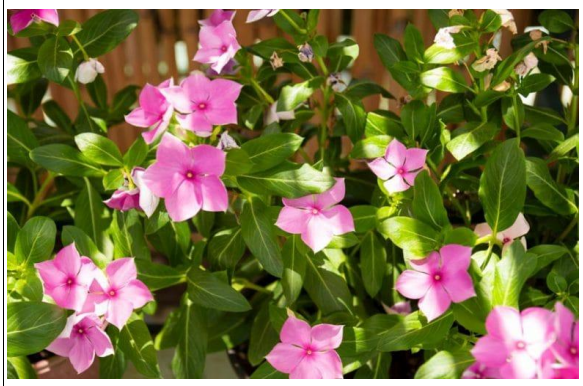
Azadirachta indica A. Juss.: Nimbolide [17–18, 26–29].

Parameter	Information
Scientific name	Azadirachta indica A. Juss.
Family	Meliaceae
Image	
Common name	Neem
Major phytochemicals	Nimbolide and other limonoids
Chemical class	Limonoids
Major constituent discussed	Nimbolide
Breast-cancer models studied	Breast-cancer models are discussed: evidence from other cancer models is contextual and not breast-cancer-specific
Experimental models	Predominantly laboratory and preclinical studies

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Antiproliferative activity	Investigated for effects on proliferation and cell-cycle control
Apoptosis induction	Apoptosis-associated pathways have been investigated
Molecular pathways investigated	NF-κB, STAT3, oxidative stress and cell-cycle control
Research limitations	Evidence is predominantly preclinical: crude extracts vary by plant part, geography and extraction method
Clinical evidence	Clinical translation is limited: human therapeutic efficacy is not established
Future research scope	Chemically defined preparations, standardisation, pharmacokinetics, safety and breast-cancer-specific validation

Catharanthus roseus (L.) G. Don: Vinca Alkaloids [19–21].

Parameter	Information
Scientific name	Catharanthus roseus (L.) G. Don
Family	Apocynaceae
Image	
Common name	Madagascar periwinkle
Major phytochemicals	Vincristine and vinblastine
Chemical class	Indole alkaloids / vinca alkaloids

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Major constituents discussed	Vincristine and vinblastine
Experimental models	Multiple cancer models and clinical oncology evidence for purified pharmaceutical alkaloids
Mechanism	Bind tubulin and disrupt microtubule dynamics, leading to mitotic arrest and cell death
Anticancer evidence	Purified vinca alkaloids are established anticancer medicines
Research limitations	Clinical status applies to standardized pharmaceutical products, not crude C. roseus extracts
Clinical evidence	Strong pharmacology and clinical oncology evidence for purified vincristine/vinblastine
Future research scope	Illustrates the importance of isolation, mechanism-based development, dose optimization, toxicology and clinical validation

Detailed Experimental Evidence [1–3, 7–12, 17–21].

Plant/constituent	Typical models	Endpoints	Interpretation
Curcumin	MCF-7, MDA-MB-231 and others	Viability, apoptosis, cell cycle, migration	Consistent preclinical activity: formulation matters
Withaferin A	MCF-7, MDA-MB-231: xenografts	Apoptosis, ROS, STAT3/NF-κB, tumor growth	Strong preclinical evidence
EGCG	MCF-7, MDA-MB-231 and others	Viability, apoptosis, migration, epigenetic signaling	Substantial preclinical evidence: exposure limits translation
Nimbolide	Breast and other cancer models	Apoptosis, inflammatory pathways, proliferation	Promising preclinical candidate
Vincristine/vinblastine	Multiple cancers: clinical oncology	Microtubule disruption, mitotic arrest	Purified agents clinically established

Molecular Mechanisms of Five Herbs as follow [1–3, 7–13, 17–21].

Plant	Major compound/class	Major pathways/processes	Cellular outcome
C. longa	Curcuminoids	NF-κB, PI3K/AKT, STAT3, Wnt/β-catenin	Apoptosis: reduced proliferation/migration

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W. somnifera	Withanolides	STAT3, NF-κB, ROS/redox, cytoskeletal pathways	Apoptosis: stress responses: reduced growth
C. sinensis	EGCG/catechins	PI3K/AKT, cell-cycle and epigenetic targets	Reduced proliferation: apoptosis
A. indica	Nimbolide/limonoids	NF-κB, STAT3, apoptosis-associated pathways	Reduced proliferation: cell death
C. roseus	Vinca alkaloids	Tubulin/microtubule dynamics	Mitotic arrest: apoptosis

Human and Translational Studies of Anticancer Potential Herbs

The key question in translation involves bridging experimentation and clinical effectiveness. Curcumin has been investigated at the clinical level, including combination treatment, but the effectiveness of curcumin in breast cancer has not yet been determined. There have been observational studies and preventive/biomarker studies for green tea, but no definitive therapy studies. There is far less evidence for the use of withaferin A and nimbolide as breast cancer therapies. The purified vinca alkaloids present an alternative pathway from natural product discovery to anticancer agents. [5, 14–16, 22, 23]

Plant/compound	Human evidence	Reasonable conclusion	Not justified
Curcumin	Early clinical/adjunctive studies	Feasibility and selected biological signals	Established breast-cancer efficacy
Green tea/EGCG	Observational and biomarker/prevention studies	Potential associations warrant study	Treatment of established cancer
Withania/withaferin A	Limited cancer-specific evidence	Preclinical rationale	Clinical efficacy
Neem/nimbolide	Very limited translation	Preclinical rationale	Human therapeutic efficacy
Vincristine/vinblastine	Extensive clinical use	Purified agents are established anticancer drugs	Crude C. roseus as equivalent therapy

Safety, Standardization and Drug-Herb Interaction

Safety considerations need to be considered alongside claims of efficacy. The composition of herbal extracts is dependent on factors such as the species used, the variety, the part of the plant used, the location, the harvesting point and method of extraction. In the absence of chemical standardization, reproducibility is impossible. Drug-herb interaction is critical in oncology because patients undergoing treatment might be using cytotoxic drugs, endocrine drugs, targeted drugs, anti-coagulant drugs and supportive drugs. [26, 27, 29]

Research Gaps and Future Directions

1) Authentication and voucher of botanicals is necessary.
2) Identification of plant material, extraction solvent, extraction yield and chemical profile should be reported.
3) The difference between whole extracts and isolated compounds/fractions should be stated clearly.
4) Results need to be reproduced using biologically different breast-cancer models.
5) Negative controls are necessary to establish selectivity.
6) Blank extract control needs to be performed when using MTT and other colorimetric methods.
7) Target-specific experiments need to prove the underlying mechanism.
8) Pharmacokinetic studies should be carried out to determine whether the concentration used in vitro can be achieved in vivo.

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9) Additive effect should not be mistaken for synergistic effect in combination studies.
10)Pre-clinical and clinical translation needs standardization of preparation, dose administration and trial design.

IV. LIMITATIONS OF THE CURRENT REVIEW

Five plant species have been chosen as examples of phytochemical categories and translational phases and cannot be considered as a complete set of medicinal plants studied in relation to breast cancer. The experiments vary from one another regarding the composition of extracts, dosages, time of exposure, cell lines, test procedures, and criteria used, hence comparison between them is not possible. [26–29]

V. CONCLUSION

Medicinal plants offer numerous chemical frameworks of high preclinical activity concerning breast cancer, but there is a great difference in the maturity of evidence. Curcuminoids and withaferin A are backed up by considerable laboratory evidence, EGCG and nimbolide are preclinical or preventive agents, while vinca alkaloids represent the most evident success story of anticancer plant-based drugs development. The future relies on the standardization, selectivity and reproducibility of pharmacology, proper exposure and validation. [1–3, 7, 11, 17, 19–21, 26–29]

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