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NEW (NATURAL, EFFICIENT AND WELFARE) THERAPEUTIC APPROACH FROM INDIAN AYURVEDIC SYSTEM FOR TNBC, TO ADDRESS AN UNMET MEDICAL NEED

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ABSTRACT

Among all breast cancer subtypes, triple-negative breast cancer (TNBC) has the worst outcomes. It is likely to recur and metastasize. Due to a lack of expression of the canonical molecular targets, conventional chemotherapeutic agents, radiotherapy and surgery have been the only options for treating this cancer. The phytochemicals derived from natural compounds have shown very significant inhibitory effects on TNBC. The advantages of natural compounds include lower toxicity, minimal side effects, and ease of accessibility. There is evidence that secondary metabolites found in natural products can inhibit TNBC. These include alkaloids, terpenoids, steroids, flavonoids, and flavonols. They may also help uncover new cancer-fighting strategies through their compositions. A review of this study may be able to help us understand how natural substances and medicinal herbs can decrease specific tumor types. Moreover, it will contribute to the development of new and highly efficient antitumor therapies for TNBC.

KEY WORDS: TNBC, Phytochemicals, Herbal Plants, Antitumor therapy

INTRODUCTION

Due to the lack of ER, PR, and HER-2 overexpression, triple-negative breast cancer (TNBC), which affects 20% of BC patients, has lower survival rates (Giovannelli P et al., 2023) Due to the molecular heterogeneity of tumour cells, TNBC is much more aggressive and differentiated than other subtypes. Based on gene expression, TNBC is categorised into six subtypes: luminal androgen receptor (LAR), mesenchymal stem-like (MSL), basal-like 1 (BL1), basal-like 2 (BL2), and mesenchymal and immune modulatory (IM) (Mir M & Qayoom H., 2023). The development of drug resistance, tumorigenesis, and epithelial-to-mesenchymal transition (EMT) are all directly correlated with all of these subtypes. (Gooding A & Schiemann W., 2020). Currently, the only treatment option for TNBC is surgery followed by radiation therapy. Chemotherapy's limited applicability for TNBC is a result of both its high toxicity and poor therapeutic outcomes. TNBC is distinct from other forms of invasive breast cancer in that it grows more quickly, spreads more quickly, has fewer treatment options, and has worse prognoses. TNBC has extremely aggressive and metastatic characteristics that are associated with a poor prognosis and higher mortality due to the lack of effective treatment (Kumar H et al., 2023). Following diagnosis, surgery and radiation therapy comprise the primary care for TNBC. Immunotherapy and anticancer medications continue to be taken into consideration as complementary treatment options. Chemotherapy only exhibits a good response in the early stages; later chemotherapy treatments cause recurrence.

Natural compounds are a valuable source for the development of new drugs and a vast reservoir of techniques for the treatment of disease in humans. Natural substances like paclitaxel, camptothecin derivatives (docetaxel, irinotecan), and other anti-tumor medications continue to be crucial in the field of tumour treatment (Wu J et al., 2023). Additionally, many naturally occurring

substances that are pharmacologically active, like quercetin and curcumin, are important in the development of antitumor or combined therapeutic chemotherapy drugs against tumours, as well as in enhancing patient survival (Islam M et al., 2023).

Natural substances are therefore a crucial component of oncology drug research. In order to assess the adjuvant role and viability of natural compounds as a future treatment for TNBC tumours, we have compiled and summarised the literature on the beneficial effects of natural compounds in TNBC treatment in recent years.

INDIAN AYURVEDA: NEW TREATMENT PARADIGM FOR CANCER

Ayurveda, the science of life, (Ayu=Life, Vid=Science) with the holistic approach to health and personalized medicine is a part of ageless Vedic heritage of India, defines that our whole-body wellness is determined by a delicate balance of three elements, the doshas (named vata, pitta and kapha), and a variety of herbs can be used for correcting, improving and innovating such balance for health care and cure. With 3000 years of experience passed through several generations, principles of Ayurveda are greatly trusted and recruited for supporting health, disease prevention and therapeutics (Kaul S & Wadhwa R., 2017). Owing to improved living, food and medical standards, the human average lifespan has increased over the years, which has raised concerns about rapidly increasing old age populations in several developing parts of the world. Allied outcomes of this are the new challenges to deal with a variety of old age pathologies such as cancers. In addition, the current scenario of industrialized lifestyle wherein we are using a large amount of chemicals and environmental pollution in a variety of forms has widely escalated incidence of these diseases.

TNBC is the breast cancer subtype with the worst prognosis, and it has a strong invasive and metastatic capacity and easily invaded into blood vessels, increasing the recurrence rate. Due to the lack of expressions of ER, PR and HER2, endocrine and targeted therapies achieve comparatively poor outcomes (Yin L et al., 2020). Therapeutic methods for TNBC are much more limited compared with other breast cancers (Liao M et al., 2022). So, there arise a need for identification of new therapeutic approach with natural compounds due to following reasons:

(I) Due to molecular heterogeneity and aggressive nature of tumor, patient shows poor survival (Tierno D et al., 2023) but, due to efficiency of natural compounds to target multiple signalling pathways, they can improve the survival of patients with diseased condition (Almatroodi et al., 2021) (Choudhary S et al., 2018)

(II) TNBC patients are more likely to develop metastases and relapse than patients with other breast cancer subtypes which is responsible for tumor progression and increasing the severity of disease (Zajac K. et al., 2023) Natural compounds inhibit TGF-β signalling pathway responsible for metastases (Hashem S et al., 2022), downregulates the mesenchymal markers responsible for EMT transition such as Snail, Slug and Vimentin (Wang W et al., 2019).

(III) Because of the absence of specific treatment guideline for TNBC, it is managed with the standard treatments such as chemotherapy, radiotherapy and surgery; however, such treatment leaves them associated with local and systemic relapse (Subhan M. 2023). Also, the standard treatments may come with side effects including nephrotoxicity, myelosuppression, leukopenia, neutropenia, thrombocytopenia, oral mucosal membrane inflammation, haemoglobin deficiency, general ill health with emaciation, loose motion, nausea etc. (Nandy S & Thakur S., 2023). Natural compounds show chemo protective, bystander inhibitory, radio protective and radiomitigative properties (Hasan M et al., 2023) (Vukmirovic D. 2023).

(IV) chemotherapy and radiotherapy remain the standard clinical therapies for TNBC where tolerance to chemotherapy severely affects the prognosis of patients with rapid development of drug resistance mechanisms and Chemo resistance is a major cause of treatment failure. This issue affects the patients' recovery and adds a tremendous decrease in the survival rate. Most of patients develop resistance during chemotherapy (acquired resistance) or de novo lack of therapeutic response (primary resistance). Through acquired resistance, the presence of processes such as drug inactivation, drug target alteration, cell death inhibition, drug efflux, DNA damage repair, epigenetic alterations and epithelial-mesenchymal transition (EMT) are observed (Jurj A et al., 2020). Whereas, Natural compounds are increases drug uptake by tumor cells, decreasing drug metabolism by enzymes (e.g. cytochromes and glutathione-S-transferases), and reducing drug efflux are

some of the mechanisms by which polyphenols increase the sensitivity of cancer cells to chemotherapeutic agents (Maleki Dana P et al, 2022).

(V) Cost of the cancer treatment is very high due to tumor heterogeneity and systemic relapse (Mehrotra R & Yadav K, 2022). With the help of the natural compounds we can overcome this situation due to their abundant source and multiple molecular targets.

Active ingredients from Natural compounds can be used for the treatment of highly aggressive subtype of the breast cancer Triple negative breast cancer. Indian Ayurveda, has blessed us with innumerable plants which can be used to treat cancer. These medicinal plants are responsible for producing various phytochemicals which provide immunity to combat plant disease. Phytochemical study of medicinal plants is indispensable to identify the presence of active constituents in them. Phytochemicals also termed secondary metabolites comprise of alkaloids, flavonoids, steroidal lactones, saponins, tannins, terpenoids, etc. Which exhibit medicinal as well as pharmacological activities such as antibacterial activity, anti-inflammatory effects (Rex J et al., 2018). Due to emerging safety records of herbal medicines in comparison to chemical drugs, medicinal plants-based drugs have regained popularity for treating even the chronic human illness. Singh M et al., 2022 have suggested that within this last three decades, cancer causing genes called oncogenes, cancer-suppressing genes (tumor suppressor genes), cancer growth factors (such as epidermal growth factor and vascular endothelial growth factor), cancer-promoting enzymes (such as cyclooxygenase [COX]-2, matrix metalloproteinase 9, inducible nitric oxide synthase), and cancer-causing protein kinases (AKT, mitogen-activated protein kinase [MAPK], protein kinase C) have been identified as targets. List of various herbs that are targeting these molecular targets have been listed below in **Table: 1**

Table:1 Molecular targets of selected Ayurvedic plants (Garodia P et al., 2007)

Sr. No.	MOLECULAR TARGETS	TRANSCRIPTION FACTORS		HERBS
I	Transcription Factors	1) Nuclear Factor kB	1.	Curcuma longa
			2.	Withania somnifera
			3.	Boswellia serrata
			4.	Aloe vera
			5.	Allium sativum
			6.	Saussurea lappa
			7.	Ocimum sanctum
			8.	Plumbago zeylanica
			9.	Cydonia oblonga
			10.	Brassica oleracea
			11.	Semicarpus anacardium
			12.	Phyllanthus amarus
			13.	Rumex crispus
			14.	Punica granatum
			15.	Coriabdrum sativum
		2) Signal Transducer and Activator of Transcription (STAT)-3	1.	Curcuma longa
			2.	Citrullus colocynthis
			3.	Indigofera tinctria
		3) Nrf-2	1.	Curcuma longa
			2.	Vitis vinifera
II	Growth Factor	1) Epidermal Growth Factor (EGF)	1.	Curcuma long

		2)	Transforming Growth Factor β	1.	Curcuma longa
		3)	Vascular Endothelial Growth Factor	1.	Curcuma longa
				2.	Boswellia serrata
				3.	Indigofera tinctria
				4.	Plumbago zeylanica
				5.	Vitis vinifera
				6.	Gmelina arborea
				7.	Commiphora mukul
		4)	Her2/neu Receptors	1.	Aloe vera
				2.	Rumex crispus
		5)	Androgen receptor	1.	Curcuma longa
				2.	Aloe vera
				3.	Vitis vinifera
		6)	EGF-R	1.	Curcuma longa
		7)	Estrogen Receptor α	2.	Curcuma longa
		8)	Fas-R	3.	Curcuma longa
III	Invasion/Metastasis	1)	Matrix Metalloproteinases	1.	Curcuma longa
				2.	Boswellia serrata
				3.	Aloe vera
				4.	Plumbago zeylanica
				5.	Rumex crispus
				6.	Gmelina arborea
				7.	Commiphora mukul
				8.	Indigofera tinctria
				9.	Dysoxylum binectrariferum
				10.	Salvia officinalis
				11.	Zingiber zerumbet
		2)	Inducible Nitric Oxide Synthase	1.	Curcuma longa
				2.	Phyllanthus amarus
				3.	Cydonia oblonga
				4.	Vitis vinifera
				5.	Tribulus terrestris
		3)	Nitric Oxide	1.	Saussurea lapparis
				2.	Boswellia serrata
				3.	Nigella sativa
				4.	Aegel marmelos
				5.	Cydonia oblonga
		4)	Cyclooxygenase 2	1.	Curcuma longa
				2.	Withania somnifera
				3.	Boswellia serrata

				4.	Plumbago zeylanica
				5.	Phyllanthus amarus
				6.	Vitis vinifera
				7.	Coptis teeta
				8.	Tribulus terrestris
				9.	Tiospora smilacina
				10.	Commiphora mukul
				11.	Indigofera tinctria
				12.	Salvia officinalis
				13.	Zingiber zerumbet
				14.	Nigella sativa
				15.	Cinnamomun cassia
				16.	Curcuma zedoary
IV	Inflammatory Cytokines	1)	Tumor Necrosis Factor **α**	1.	Curcuma longa
				2.	Saussurea lappa
				3.	Curcuma zedoary
		2)	Interferon-c	1.	Cydonia oblongas
		3)	Interleukin (IL)-1	1.	Curcuma longa
				2.	Saussurea lappa
				3.	Phyllanthus amarus
				4.	Vitis vinifera
		4)	IL-4	1.	Gmelina arborea
				2.	Medicago sativa
				3.	Curcuma zedoary
				4.	Indigofera tinctria
		5)	IL-6	1.	Curcuma longa
				2.	Vitis vinifera
		6)	IL-8	1.	Curcuma longa
				2.	Saussurea lappa
				3.	Vitis vinifera
V	Enzymes	1)	Adenosine Triphosphatase	1.	Curcuma longa
				2.	Alstonia scholaris
		2)	Glutathione-S-Transferase	1.	Curcuma longa
VI	Apoptosi	1)	Bcl-2	1.	Curcuma longa

				2.	Boswellia serrata
				3.	Plumbago zeylanica
				4.	Brassica oleracea
				5.	Vitis vinifera
				6.	Gmelina arborea
				7.	Commiphora mukul
				8.	Brassica compestris
				9.	Indigofera tinctria
				10.	Zingiber zerumbet
		2)	Bcl-xl	1.	Curcuma longa
				2.	Boswellia serrata
				3.	Plumbago zeylanica
				4.	Brassica oleracea
				5.	Vitis vinifera
				6.	Brassica compestris
		3)	Bax	1.	Vitis vinifera
		4)	Survivin	1.	Plumbago zeylanica
				2.	Vitis vinifera
		5)	Caspases	1.	Aloe vera
				2.	Cymbopogon winterinus
				3.	Cymbopogon martini
				4.	Vitis vinifera
				5.	Cymbopogon citrus
VII	Cell Cycle	1)	p53	1.	Curcuma longa
				2.	Vitis vinifera
		2)	p21Cip1/WAF1	3.	Vitis vinifera
				4.	Gmelina arborea
				5.	Glycyrrhiza glabra
				6.	Indigofera tinctria
		3)	Cyclin D	1.	Curcuma longa
				2.	Boswellia serrata
				3.	Plumbago zeylanica
				4.	Vitis vinifera
				5.	Commiphora mukul
				6.	Indigofera tinctria
				7.	Dysoxylum binectrariferum
				8.	Salvia officinalis
				9.	Zingiber zerumbet
				10.	Vitis vinifera
				11.	Gmelina arborea

VIII	**Others**	1)	Histone Deacetylase	1.	Curcuma longa
				2.	Pisum sativum

Due to their multiple targets, Herbal plants and their natural compounds can thus effectively be recommended for supporting the therapy of various cancers, including TNBCs.

CONCLUDING REMARKS

Compared to other types of breast cancers, TNBCs account for 10–24% of all breast cancers and are the most aggressive. ER, PR and HER2 receptors are not expressed in these tumors (Maqbool M et al., 2022). Due to the lack of target receptors in TNBCs and the lack of specific promising therapeutic targets, hormonal/HER2 targeted therapies are not effective. The only treatment option for such "no-option" breast cancer patients is to administer cytotoxic chemotherapeutic drugs (Al-Mahmood S et al., 2018). Furthermore, TNBCs are heterogeneous, show early recurrence, develop resistance, metastasize rapidly, and are associated with poor prognoses. Using classical chemotherapeutic drugs such as anthracyclines, cyclophosphamides, taxanes, and platinum-based compounds for treating TNBCs is associated with toxic side effects and induced resistance (Bravo Bonilla M., 2022).

Several naturally occurring compounds have been identified that are effective anticancer drugs with much fewer side effects. Additionally, these phytochemicals were effective against cancer, reduced the amount of cytotoxic drugs required for anticancer effects, and were associated with fewer side effects when combined with classical anticancer drugs (Varghese E et al., 2018). Several herbal plant extracts and their compounds have been studied for their potential to fight cancer in this study. Cancer can be treated with these organic ingredients. Gene modifications, deletions, cell proliferation, genetic alterations, and excessive protein synthesis can be controlled by these components. The use of natural compounds is suggested as an alternative to chemotherapeutic drugs. Bioaccessibility and bioavailability of biological agents, their nontoxicity to normal cells, and their antitumor/anti-metastatic potential make natural agents potent chemopreventive and chemotherapeutic agents. A number of studies on cells and animal models of TNBC have shown suppressive effects of herbal medicine extracts and bioactive compounds, including flavonoids, terpenes, carotenoids, alkaloids, retinoids, and lignans (Arzi L et al., 2022). A number of phytotherapy agents exhibit anti-proliferative, proapoptotic, anti-migratory, and anti-invasion properties. Co-administration of natural compounds and chemotherapy agents facilitates chemotherapy's effectiveness. Combination therapy may have adverse effects due to pharmacodynamic and pharmacokinetic interactions between herbs and chemotherapy. Thus, clinical trials evaluating natural bioactive compounds are a potential future development. It appears that herbal extracts and derivatives could be a promising TNBC treatment, especially in the absence of effective targeted therapies.

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