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ROLE OF AYURVEDA IN BREAST CANCER TREATMENT

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Ayurveda, which means science of long life, is at least a 5,000-year-old system of Indian medicine (1500–1000 BC) designed to promote good health and longevity rather than to fight disease and was practiced by physicians and surgeons (called bheshaja or vaidya). Ayurveda, the holistic science has multi-targeted herbal drugs, adjuvant therapy to offer in addition to the conventional medicine in the management of this type of cancer.[1]

BREAST CANCER

Breast cancer is the most common malignancy among women globally and in India. The higherprevalence of advanced breast cancer (ABC) in elderly women is attributable to delayed diagnosis, lack of sufficient health care resources, Variablity in disease presentation and progression and high costs for conventional treatment.[2] Cancer is a malignant growth or tumour resulting from an uncontrolled division of cells. Cancers figure among the leading causes of morbidity and mortality worldwide, with approximately 14 million new cases and 8.2 million cancer related deaths (W.H.O).[3] Many promising remedies for breast cancer are included in Ayurveda, the Indian system of medicine. The present review concentrates on the available literature found in Ayurveda regarding plants and breast cancer.[4]

EPIDEMIOLOGY

For every two women newly diagnosed with breast cancer, one woman dies of it in

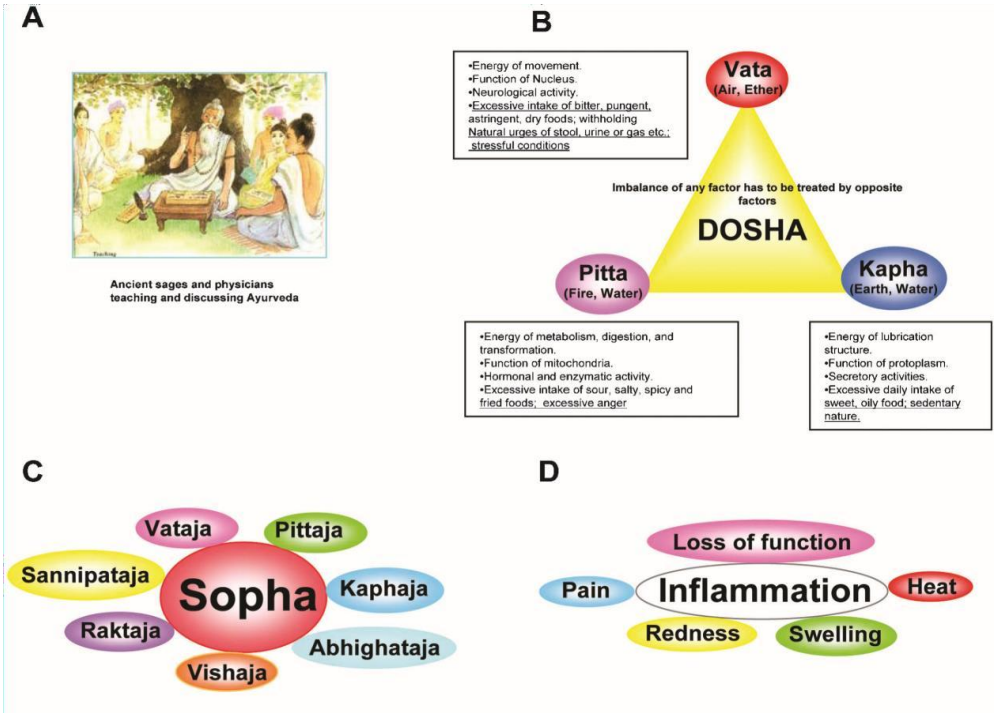
India.[5][6][7] Breast cancer in females accounts for over 50% of all cancer deaths in India.[8] Breast cancer is the most common cancer in women in India and accounts for 27% of all cancers in women.[9] The incidence rates in India begin to rise in the early thirties and peak at ages of 50-64 years.[10] Breast cancer nowadays is a common cancer among the rural Indian population with an age-adjusted rate and mortality as high as 25.8 and 12.7 per 100,000 women respectively.[11] In India, the incidence of breast cancer is increasing each year and estimation approximates 200,000 women will be affected annually by 2030.[12]

ECONOMIC BURDEN

The International Agency for Research on Cancer GLOBOCAN project[13] has predicted that India's cancer burden will nearly double in the next 20 years, from slightly over a million new cases in 2012 to more than 1·7 million by 2035.

AYURVEDIC CONCEPT OF HEALTH

According to ayurveda, most diseases connected with the psychophysiologic and pathologic changes in the body are caused by imbalance in three different dosha (ie, vata, pitta, and kapha).[16] The fundamental aim of ayurvedic therapy is to restore the balance between these three major body systems.[14,15,17-19] Any imbalance can lead to inflammation (also called sopha). The balanced coordination of body, mind, and consciousness is the ayurvedic definitionof health. (Figure 1).



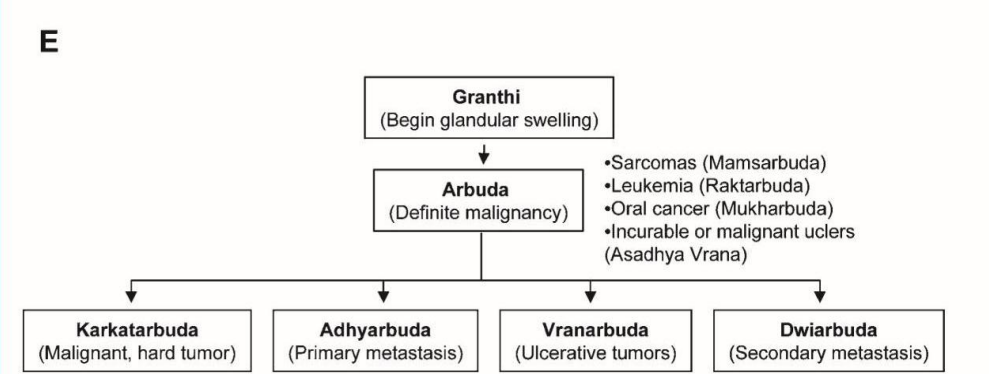


Figure 1: Ayurvedic concept of inflammation and cancer. A, Teaching of ayurveda in ancient times. B, The role of tridoshas in the pathogenesis of the disease. Aggravating factors are underlined. C, Different types of sophas (inflammation/swelling). D, Different manifestations of inflammation. E, Development and progression of cancer through different stages.[14-19]

AYURVEDIC APPROACH OF BREAST CANCER

Based on the descriptions of symptoms and signs of the disease condition, the following conditions can be compared with Gynecological cancers.

Kunapa granthi artavadushti, Granthibhuta artavadushti, Sannipataja pradara, Rakta arbuda, Mamsa arbuda etc.[20] Raktarbuda is a fast growing tumour, presents with vitiated bloody discharge(Figure 1E). Mamsarbuda presents a painless, stony hard, smooth, fixed swelling, which never suppurates. Both these Arbuda are labelled as incurable. Based on the clinical features, both of these tumours can be considered as Malignancies.[21] It can involve Dhatus like Mamsa and Rakta due to vitiation of Tridosa.[22] One who lives according to Dinacharya, Nishacharya, Ritucharya as described will never suffers from severe disorders caused by environmental, seasonal, or external factors otherwise he would land up with any diseases.[23]

PATHOPHYSIOLOGY OF BREAST CANCER

Due to unbalanced diet and inappropriate behaviour. The signaling process, associated with cancer pathology, includes metabolic changes in cellular components such as aerobic glycolysis, mitochondrial DNA degradation, alteration in the electron transport chain, and epigenetic changes regulating genomic expressions, finally resulting in abnormal cell proliferation, angiogenesis, metastasis. The BRCA1 & BRCA2 genes have been identified as predisposing genes for hereditary factors for breast cancer pathogenesis. The highest incidence of breast cancer is seen in post-menopausal women.[24]

The highest incidence of breast cancer is seen in post-menopausal women.[24] The majority of such tumors are fast-growing with lymph node metastasis and have triple-negative molecular subtypes.[25] Triple-negative breast cancer maintains high levels of ATPs and around 80–90 % of their energy supply comes from intracellular fatty acid beta-oxidation.[26] Malignant cells are demarcated into three stages which include initiation, promotion, and progression.[27] Oxidative stress plays a central role in all these stages. It induces DNA base modification, the rearrangement of DNA sequence, miscoding of DNA lesions, gene duplication, and the activation of oncogenes in the initiation stage. This is followed by the promotion stage rendered by the ROS in ceasing cell to cell communication and the stimulation of the secondary messenger system.

Finally, ROS influences proliferation, apoptosis, senescence leading in the development of cancer. With progress in advance research regarding understanding the mechanism of pathogenesis and novel targets, newer treatment guidelines are emerging every year with the intention to minimize the associated adverse effects of conventional methods of treatment. The adverse effects of existing treatment modalities include nausea, loss of appetite, vomiting, stomatitis, diarrhea, constipation, bleeding piles, fever, skin, and nail discoloration[28] with an overall bad score of "Quality of life". Females taking anti-estrogen therapy experience adverse effects like vein thrombosis, cataract formation, endometrial carcinoma, menstrual disorders, and hot flushes. Targeted therapies have limitations for developing drug resistance in cancer cells.[29]

SAMPRAPTI: THE AYURVEDIC DESCRIPTION OF PATHOPHYSIOLOGY OF BREAST CANCER

The samprapti (pathogenesis) occurs due to various causes, such as repeated exposure to environmental toxins, which are pitta provoking factors at the deeper cellular level. The increased pitta at the cellular level can cause micro inflammatory changes, which disturb the cellular components of agni called pilu agni and pithar agni. Due to slow pilu agni, pithar agni produces poorly formed tissue. In Ayurvedic pathogenesis, vata is the active dosha and is involved in the process of metastasis. Kapha being heavy and gross is responsible for the abnormal growth of the cells creating the malignant tumor, and the tejas component of pitta enhances the metabolic activity of the cancerous cells. (Figure 2)

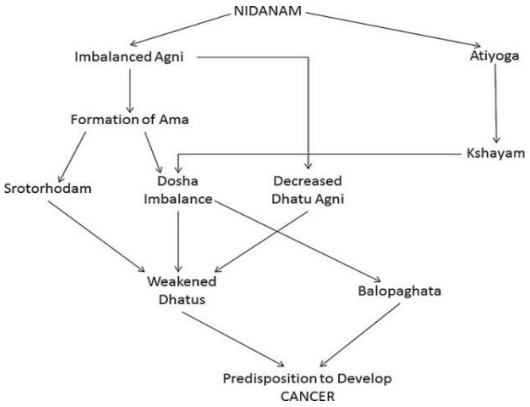


Figure 2: Samprapti - The Ayurvedic description of the pathophysiology of cancer.[33]

AYURVEDIC CONCEPT OF TREATMENT

Formulations are being used as an adjuvant along with chemotherapy and radiotherapy to overcome their toxic reactions and to improve the therapeutic efficacies. These formulations are mostly polyherbal mixtures combined with a metallic preparation, known as "Bhasma" in Ayurveda but with help of current bioinformatics tools, significant results are being published for each plants constituent in these Ayurvedic compound formulations, which are already in clinical use.[30] These formulations may normalize the function of multiple deregulated proteins found in breast cancer cells.[31]

Based on the symptoms, the chosen ayurvedic drugs for the management of breast cancer targets the agni (digestive power), vata-shamak (anti-inflammatory and anti-oxidants), and enhance ojas (immunomodulators).[32] The treatment modalities are also associated with detoxification processes of the body by both pharmacological and non-pharmacological processes like panchkarma therapies, enhancing the process of cellular autophagy to remove the accumulated "Ama" (modified non-functional proteins). These processes inactivate the existing free radicals (superoxide, hydrogen peroxide, and hydroxyl radical), to break the chain reaction, by directly interacting (electron transfer) with them and by enhancing the endogenous antioxidant enzymes like superoxide dismutase, catalase and reduced glutathione.(Figure 3)

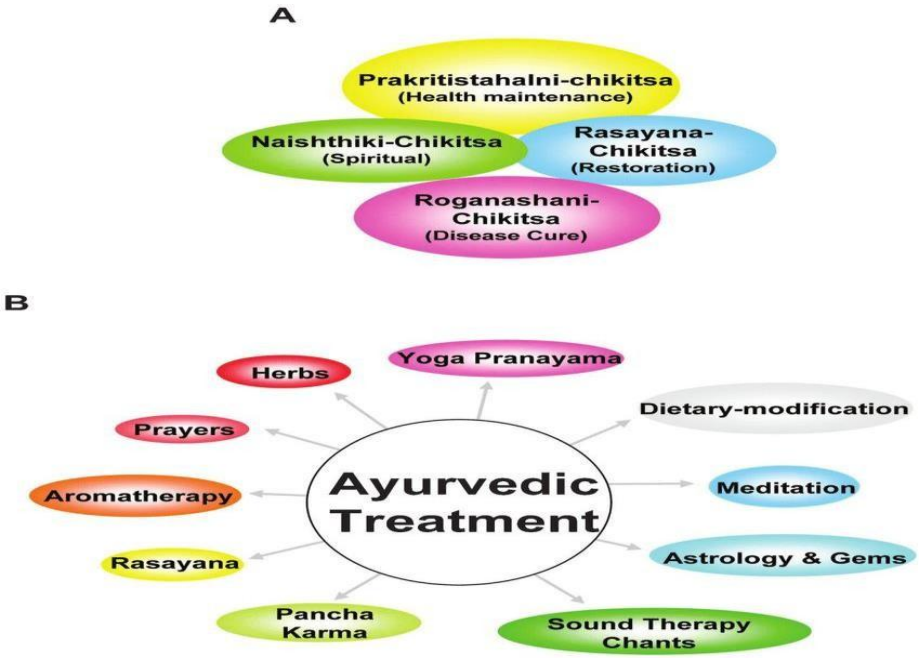


Figure 3: Ayurvedic concept of treatment of inflammation and cancer. A, Multiple approaches for the prevention and treatment of cancer. B, Different therapeutic modalities currently employed for the treatment of cancer.[35,36]

AYURVEDIC TREATMENT INCLUDED PROCEDURES USED IN PANCHKARMA[33]

ANTIOXIDANT EFFECT

This modality of treatment is a total body detoxifying procedure, particularly to eliminate toxins deeply situated in all the tissues and organs, often adopted in Ayurvedic therapy with remarkable effect. These procedures are accompanied by oil-based treatment modalities, strict diet and lifestyle practices. Apart from Panchakarma, the patient was also treated with allied procedures such as Shirodhara and Shiropichu[34] and Pinda Sweda.[35] Shirodhara and Shiropichu are effective in stress management[36], which is considered as evident risk factorin TNBC. Pinda Sweda is a type of sudation in which a bolus of rice cooked with milk and herbal decoctions[35] is applied on the targeted part of the body such as chest region in this case. Significant improvement in the Quality of Life and progression free survival have been reported in patients including TNBC patients undergoing yearly Panchakarma treatment.

Reduction in inflammatory response based on serum cytokines, and ROS generation in erythrocytes extracts have also been studied in patients treated with Panchakarma.[37] Similarly, immunological and metabolic responses in a therapeutic course of Basti in obesity have documented modulation of immune responses by regulating pro-inflammatory cytokines,

immunoglobulins and functional properties of T-cells, which are associated with a reduction in the body weight and its maintenance even after three months of treatment.[38] Pharmacokinetic aspect of Lekhana Basti has also been analysed with the help of HPLC which suggests the absorption of phytochemicals from the Basti formulations in the systemic circulation.[39]

Major molecular therapeutic targets for Breast cancer therapy

To date, 41 multitudes of genes have been identified for direct or indirect involvement of methylation in breast carcinoma and this number is continuously increasing.[40] A variety of herbs targeted at specific molecules for the prevention of breast cancer are broadly classified as an anti-inflammatory, Immune system activating, Endocrine suppressor, Tumor suppressor, Glut-1 inhibitor, Aromatase inhibitor, and Lectin containing plants. The majority of these molecular therapeutic targets have been shown to possess promising broad-spectrum anticancer activities.

Anti-Inflammatory therapeutics family

Herbs described in Table1 suppresses Nuclear factor-kappa B (NFκB), a transcription factor regulating the expression of various inflammatory genes, cytokine production, and cell survival.[41] These proteins have been identified as COX-2, cyclinD1, MMPs, iNOS, HER2, EGFR, BCL-2, BCL-XL, and TNF alpha. They inhibit carcinogenic activation by directly inhibiting the aryl hydrocarbon-induced CYP1A1 expression and restrain carcinogen initiation, promotion, and progression. Inhibitor of apoptosis protein (IAP1) is a class of proteins that mainly cause intracellular damage leading to cancer if mutated or improperly synchronized. These can be found in herbs and have been described in Table1. Bcl-2 is a regulator protein that controls cell death (apoptosis) inhibited by herbs depicted in Table1. The Inhibitor- ofapoptosis protein (cFLIP) inhibited by herbs is a master anti-apoptotic controller and resistance feature that suppresses tumour necrosis factor-α (TNF-α). Proliferative genes (cyclin D1, cMyc) inhibited by plant species are concerned with cell proliferation, leading to the formation of cancer.[42] Matrix metalloprotease (MMP-9) inhibited by plant species are thought to also play a chief role in cell behaviors such as cell proliferation, migration (adhesion/dispersion), differentiation, angiogenesis, apoptosis, and host defence.[43] Cyclooxygenase (COX-2) inhibited by plant species has been shown to reduce the incidence of cancers and pre-cancerous growths.[44] Cytochrome p450 (CYP7A1) that produce toxic metabolites that facilitate increased risks of cancer are reduced by these

herbs. BCL2-related protein A1, Bfl1/A1inhibited by plant species, act as anti- and pro-apoptotic regulators that are concerned in a wide variety of cellular activities such as embryonic development, homeostasis, and tumorigenesis.[45] Survivin protein inhibited by plants inhibits caspase activation, leadingto programmed cell death.[46]

CyclinD1 can guide oncogenes by rising anchorage-independent growth and angiogenesis via VEGF production. Cyclin D1− 1 inhibited by herbs controls numerous cellular processes which includes differentiation, proliferation, and apoptosis. Cyclin-dependent kinase 2 (cdc25) inhibited by some plant species controls the admission and progression of various phases of the cell cycle, as well as mitosis and S ("Synthesis") phase.[47] Apoptosis suppressor proteins such as B-cell lymphoma 2 (Bcl-2) control cell death (apoptosis), by inhibiting (anti-apoptotic) or inducing (pro-apoptotic) apoptosis. B-cell lymphoma-extra-large (Bcl-xL) inhibited by herbs acts as an anti-apoptotic protein by preventing the discharge of mitochondrial contents such as cytochrome c, which leads to caspase commencement and ultimately, programmed cell death.[48] C-Jun N-terminal kinases (JNKs) reduced by plant species participate in T cell differentiation and the cellular apoptosis pathway.[49] Interleukin (IL-1, IL-4, IL-6, IL-8, IL12 IL-13) inhibitors present in herbs in Table1 stimulate activated B-cell and T-cell proliferation, and the separation of B cells into plasma cells.[50] Some Caspase-3 inhibitors present in herbs play an essential role in the execution phase of cell apoptosis.[51] EGR-1 (Early growth response protein 1) inhibitors present in various plant species are required for differentiation and mutagenesis.[52] Signal transducer and activators of transcription 1 (STAT1) inhibitors have the role in controlling the expressions in survival of the cell and cell viability. Peroxisome proliferator-activated receptor gamma (PPAR-γ or PPARG) inhibitors present in the herbs described in Table1 can regulate fatty acid storage and glucose metabolism. The genes activated by PPARG encourage lipid uptake and adipogenesis by fat cells.[53] βcatenin present in herbs is a dual function protein, resulting in the regulation and coordination of cell-cell adhesion.

Table 1: Molecular target of different plants.[4]

Sr. No	Molecular target	Ayurveda name	Botanical name	Relevant Ayurvedic classical uses	Activity on breast cancer	Classical Ayurvedic reference	Reference molecular target
1.	↓NF-κB	*Guggulu*	*Commiphoramukul* (Hook. ex Stocks) Engl.	*Sopha* (oedema)	Inhibits carcinogen activation	SS.Cl.23.12	Aggarwal et al., 2006
		Rakta sarshapa	*Brassicacampestris* L.	*Sopha* (oedema)		CS.Cl.12.18	
		Krishna sarshapa	*Brassica juncea* (L.) Czern.	*Sopha* (oedema)		CS.Cl.12.98	
		Saunf	*Foeniculumvulgare* Mill.	*Sula* (pain)		BP.Haritakyadi.119	
		Kashmari	*Gmeliana arborea* Roxb.	Breast diseases		BS.368	
		Haridra	*Curcuma longa* L.	*Visarpa* (erysipelas)		VM.57.97	
		Sallaki	*Boswelliaserrata* Roxb. ex Colebr.	*Vrana*(wound)		SS.Su.25.28	
		Indravaruni	*Citrullus colocynthis (L.)*	*Vrana* (wound)		SS.Su.37.13–14	
		Draksha	*Vitis vinifera* L.	*Sula* (pain)		VD.13.18	
		Aswagandha	*Withaniasomnifera* (L.)	*Visarpa* (erysipelas)		CS.Cl.21.123	
		Bhallataka	*Semecarpusanacardium* L.f.	*Apachi* (abscess)		SG.3.11.18	
2.	↓IAP1	*Guggulu*	*Commiphora mukul* (Hook. ex Stocks)	*Sopha* (oedema)	Inhibit intracellular damage	SS.Cl.23.12	
		Draksha	*Vitis vinifera* L.	*Sula* (pain)		VD.13.18	
		Adraka	*Zingiber officinale* Roscoe	*Sopha* (oedema)		CS.Cl.12.47–48; SS.Cl.23.12	
3.	↓XIAP	*Guggulu*	*Commiphora mukul* (Hook. ex Stocks)	*Sopha* (oedema)	Inhibit apoptotic cell death	SS.Cl.23.12	
		Adraka	*Zingiber officinale* Roscoe	*Sopha* (oedema)		CS.Cl.12.47–48; SS.Cl.23.12	Obexer and Ausserlechner, 2014
4.	↓Bcl-2	*Guggulu*	*Commiphora mukul* (Hook. ex Stocks)	*Sopha* (oedema)	Controls cell death (apoptosis)	SS.Cl.23.12	Aggarwal et al.
		Rakta sarshapa	*Brassica compestris*	*Vrana* (wound)		CS.Cl.12.18	
		Krishna sarshapa	*Brassica juncea* (L.) Czern.	*Sopha*(oedema)		CS.Cl.12.98	
		Kashmari	*Gmeliana arborea* Roxb.	Breast diseases		BS.368	
		Haridra	*Curcuma longa* L.	*Visarpa* (erysipelas)		VM.57.97	Opferman and Kothari, 2018
		Draksha	*Vitis vinifera* L.	*Granthi* (cyst)		SS.Cl.18.9	
		Adraka	*Zingiber officinale* Roscoe	*Sopha* (oedema)		CS.Cl.12.47–48; SS.Cl.23.12	
5.	↓cFLIP	*Adraka*	*Zingiber officinale* Roscoe	*Sopha* (oedema)		CS.Cl.12.47–48; SS.Cl.23.12	
6.	↓cyclin D1, c-Myc	*Guggulu*	*Commiphora mukul* (Hook. ex Stocks)	*Sopha* (oedema)	Anti-apoptotic controller Inhibits cell proliferation	SS.Cl.23.12	
		Kashmari	*Gmeliana arborea* Roxb.	Breast diseases		BS.368	
		Haridra	*Curcuma longa* L.	*Visarpa* (erysipelas)		VM.57.97	
		Draksha	*Vitis vinifera* L.	*Granthi* (cyst)		SS.Cl.18.9	
		Adraka	*Zingiber officinale* Roscoe	*Sopha* (oedema)		CS.Cl.12.47–48; SS.Cl.23.12	
7.	↓MMP-9	*Guggulu*	*Commiphora mukul* (Hook. ex Stocks)	*Sopha* (oedema)	Cell proliferation, migration (adhesion/ dispersion)	SS.Cl.23.12	
		Ghritakumari	*Aloe vera* (L.) Burm.f.	*Stana vyatha / Vidradhi* (mastitis)		GN.6.8.23	Aggarwal et al.
		Adraka	*Zingiber officinale* Roscoe	*Sopha* (oedema)		CS.Cl.12.47–48; SS.Cl.23.12	
8.	↓COX-2	*Guggulu*	*Commiphoramukul* (Hook. ex Stocks),	*Sopha* (oedema)	Inhibit pre-cancerous growth	SS.Cl.23.12	
		Kashmari	*Gmeliana arborea* Roxb.	Breast diseases		BS.368	
		Haridra	*Curcuma longa* L.	*Visarpa* (erysipelas)		VM.57.97	
		Draksha	*Vitis vinifera* L.	*Granthi* (cyst)		SS.Cl.18.9	
		Bhumyamalaki	*Phyllanthus urinaria* Linn.	Gynaecological diseases		BS.Stri roga.42	
9.	↓CYP7A1	*Guggulu*	*Commiphora mukul*(Hook. ex Stocks)	*Sopha* (oedema)	Inhibit toxic metabolites	SS.Cl.23.12	Zanger and Schwab, 2013

10	↓BCL2-related protein A1, Bfl-1/A1	*Guggulu*	*Commiphora mukul* (Hook. ex Stocks)	*Sopha* (oedema)		SS.CI.23.12	
11	↓Survivin	*Guggulu*	*Commiphoramukul*(Hook. ex Stocks)	*Sopha* (oedema)	Inhibit apoptosis	SS.CI.23.12	
		Draksha	*Vitis vinifera* L.	*Granthi* (cyst)		SS.CI.18.9	
		Adraka	*Zingiber officinale* Roscoe	*Sopha* (oedema)		CS.CI.12.47–48; SS.CI.23.12	
		Haridra	*Curcuma longa* L.	*Visarpa* (erysipelas)		VM.57.97	
12	↓CyclinD1	*Draksha*	*Vitis vinifera* L.	*Granthi* (cyst)	Controls differentiation, proliferation, and apoptosis	SS.CI.18.9	
		Yastimadhu	*Glycyrrhiza glabra* L.	Gynaecological diseases		BP.CI.68.13	
		Saunf	*Foeniculumvulgare* Mill.	*Sula* (pain)		BP.Haritakyadi.119	
		Dhanyak	*Coriandrumsativum* L.	*Sopha* (oedema)		SG.2.2.65	
		Rakta sarshapa	*Brassica compestris* L	*Vrana* (wound)	Controls progression during various phases of the cell cycle	CS.CI.12.18	
		Krishna sarshapa	*Brassica juncea* (L.) Czern.	*Sopha* (oedema)		CS.CI.12.98	
13	↓cdc25	*Kashmari*	*Gmeliana arborea* Roxb.	Breast diseases		BS.368	
		Draksha	*Vitis vinifera* L.	*Granthi* (cyst)		SS.CI.18.9	
		Haridra	*Curcuma longa* L.	*Visarpa* (erysipelas)		VM.57.97	
14	↓Bcl-xL	*Draksha*	*Vitis vinifera* L.	*Granthi* (cyst)	Anti-apoptotic protein	SS.CI.18.9	
		Rakta sarshapa	*Brassica compestris* L.	*Vrana* (wound)		CS.CI.12.18	
		Krishna sarshapa	*Brassica juncea*(L.) Czern.	*Sopha* (oedema)		CS.CI.12.98	
		Dhanyak	*Coriandrumsativum* L.	*Sula* (pain)	T cell differentiation and the cellular apoptosis pathway	SG.2.2.65	
		Haridra	*Curcuma longa* L.	*Visarpa* (erysipelas)		VM.57.97	
15	↓JNKs	*Draksha*	*Vitis vinifera* L.	*Granthi* (cyst)		SS.CI.18.9	Aggarwal et al.
		Draksha	*Vitis vinifera* L.	*Granthi* (cyst)		SS.CI.18.9	
		Bhui amla	*Phyllanthusurinaria* L.	*Sula* (pain)		VD.16.50	
	↓IL-1, ↓ IL-4, ↓IL-6, ↓IL-8, ↓IL-12 ↓IL-13	*Pippali*	*Piper longum* L.	*Sopha* (oedema)	Stimulates activated B-cell and T-cell proliferation	VM.39.10; BP.CI.42.34	
16		*Yastimadhu*	*Glycyrrhiza glabra* L	Gynaecological diseases		BP.CI.68.13	
		Upakunchika	*Nigella sativa* L.	*Sula* (pain)		AH.U.34.30–31	
		Kashmari	*Gmeliana arborea* Roxb.	Breast diseases		BS.368	
		Jambira	*Citrus limon* (L.)	*Sula* (pain)		VM.65.14	
17	↓Caspase-3	*Ghritakumari*	*Aloe vera* (L.) Burm.f	*Stana vyatha* (mastitis)		GN.6.8.23	
		Kadali kanda	*Musa paradisiaca* var. sapientum (L.) Kuntze. L	Gynaecological diseases		RM.31.3; G.Ni.6.1.69	
18	EGR-1	*Haridra*	*Curcuma longa* L.	*Visarpa* (erysipelas)	Inhibits differentiation and mutagenesis	VM.57.97	
		Draksha	*Vitis vinifera* L.	*Granthi* (cyst)		SS.CI.18.9	
		Indravaruni	*Citrullus colocynthis* (L.)	*Vrana* (wound)	Role in many gene expressions related to cell survival	SS.Su.37.13–14	
19	↓STAT1	*Haridra*	*Curcuma longa* L.	*Visarpa* (erysipelas)		VM.57.97	
		Pippali	*Piper longum* L.	*Sopha* (oedema)		VM.39.10; BP.CI.42.34	
20	↓PPAR-γ or PPARG	*Haridra*	*Curcuma longa* L.	*Visarpa* (erysipelas)	Regulates fatty acid storage, and glucose metabolism	VM.57.97	
21	↓HER2	*Haridra*	*Curcuma longa* L.	*Visarpa* (erysipelas)	Reduces	VM.57.97	
		Ghritakumari	*Aloe vera* (L.) Burm.f.	*Stana vyatha* (mastitis)	progression in	GN.6.8.23	

Herbs (Table2) that reduce the HER2 receptor, a member of the human epidermal growth factor receptor (HER/EGFR/ERBB) family has been revealed to participate a significant role in the development and progression of certain aggressive types of breast cancer.[54] Akt is a serine/threonine-specific protein kinase that acts as a mediator and plays a key role in multiple cellular processes such as glucose metabolism, apoptosis, cell proliferation, transcription, and cell migration.[55] It may be inhibited by some plant species. Proto-oncogene tyrosine-protein kinase (Src) inhibitors present in herbs promote cell survival, angiogenesis, proliferation, and invasion pathways. Janus kinase 2 (JAK2) is a non-receptor tyrosine kinase inhibited by plant species declining the fusions with the TEL (ETV6) (TEL-JAK2) and PCM1 genes.[56] Nonreceptor tyrosine-protein kinase is a type of protein which accounts for transferring a phosphate group to a tyrosine residue in proteins such as ATP, to tyrosine residues. Herbs described in Table1 inhibit different inflammatory pathways by creating an environment in which the various stages of tumorigenesis including tumour initiation, proliferation and metastasis are reduced.[57] The immune system plays a big role in breast cancer management.It

not only destroys cancer cells or inhibit their growth but also promotes tumour progression and metastasis.[58] The increase in the levels of ascorbic acid, glutathione, tocopherol (Vitamin E), and the decrease in malondialdehyde provides evidence of free radical scavenging activity and antioxidant effects of different herbs is presented in Table 2[59] Mitogen-activated protein kinases (MAPK) is a chain of proteins in the cell that communicates a signal from a cell surface receptor to the DNA in the nucleus of the cell.[60] The process starts when a signaling molecule binds to the current cell surface receptor and ends when the DNA in the nucleus expresses a protein and produces some change in the outward behaviour or appearance in the cell. Signal transducer and activator of transcription 3 (STAT3) are transcription factors that mediate cellular responses to a range of cytokines and growth factors encoded by the STAT3 gene in humans.

Table 2: Molecular targets of different plants used to activate immune cells potential in Breast cancer.[4]

Sr. No	Molecular targets	Ayurveda name	Botanical name	Relevant Ayurvedic classical uses	Breast cancer activity	Classical Ayurvedic references	Reference molecular target
1.	↑ SOD, ↑ CAT, ↑ GPX	Amalaki	Emblicaofficinalis Gaertn	Rasayana (Activating Immune cells)	Reduce the frequency of chromosomal breakages, gaps, and rearrangement	CS.CI.1.2.8	Shukla et al., 2009
2.	↑ Malondialdehyde	Bilva	Aegle marmelos	Rasayana (Activating Immune cells)	Important role in cytoprotecting and membrane damage	SS.CI.28.10– 12	Singh et al., 2000
3.	↑ MAPK	Amalaki	Emblicaofficinalis Gaertn	Rasayana(Activating Immune cells)	Communicates a signal from a current cell surface receptor to the DNA	CS.CI.1.2.8	Shukla et al., 2009

Endocrine therapy for breast cancer

There are two types of endocrine therapy for breast cancer like drugs that stop estrogens and progesterone from helping breast cancer cells grow and drugs or surgery to keep the ovaries from making the hormones. Hormones like prolactin, progesterone, and estrogens are important in the regulation of breast cancer growth. The third generation Aromatase inhibitors target their action in order to reduce the production of estrogen in postmenopausal women. Aromatase is the enzyme that catalyzes the conversion of the hormone androgen into small amounts of estrogen which circulate continuously in the body. This means that fewer estrogens stop the growth of hormone-receptor-positive breast cancer cells.[61] Plant species describedin Table 3 suppress breast cancer cell proliferation.

Table 3: Molecular targets of different plants used for endocrine potential in Breast cancer.[4]

Sr. No	Molecular target	Ayurveda name	Botanical name	Relevant Ayurvedic classical uses	Activity on breast cancer	Classical Ayurvedic Reference	Reference Molecular target
1.	↓EGFR	*Indravaruni*	*Citrullus colocynthis (L.) Withaniasomnifera* (L.)	Gynaecological diseases	Suppresses breast cancer cell proliferation	VJ.3.36	Chowdhury et al., 2017
2.	↓ER-α	*Aswagandha*	*Aloe vera* (L.) Burm.f.	Gynaecological diseases		VM.14.10	Palliyaguru et al., 2016
3.	↓BCL2	*Kumari*	*Elettaria cardamomum* (L.) Maton	Gynaecological diseases		BR.P.1182–83	Reuter S et al., 2010
4.	↓cyclin D1	*Elaichi*		Gynaecological diseases	Prevention and inhibition of breast cancer growth	VM.32.18	Vutakuri and Somara, 2018

Tumor suppressor receptor family for breast cancer

The potential herbs used to prevent the growth of cancer cells have been well documented in Table 4. The Indole- 3 carbinol is a bioactive component converted to a series of oligomeric products (among which 3,3′ -diindolylmethane is a major component) supposed to be responsible Table for its biological effects in vivo. Indole- 3 carbinol present in cardamom has been shown to reduce the growth of various tumour cells, as well as those from breast, prostate[62] endometrial, and colon cancers and leukemia, induce G1/S cell-cycle arrest, and induce apoptosis[63] The cell-cycle withdrawal involves the downregulation of cyclin D1 activities which inhibits cyclin E, associated CDK2, CDK4, and CDK6 activities, and up-regulation of the expression of p15, p21, and p27. Treatment with Indole- 3 carbinol inhibited the antiapoptotic gene products, including the expression of Bcl-2, Bcl-XL function, surviving expression, IAP cell death regulator, X-linked inhibitor of apoptosis inactivation, and caspase8inhibitory proteinin cells, resulting in up-regulation of the pro-apoptotic protein Bax, the release of mitochondrial cytochrome c which activates caspase-9 and caspase-3 pathway.[64]

This agent inhibits the activation of various transcription factors in various cells NF-κB expression, SP1 mediated activation, estrogen receptor domains, the binding of the androgen receptor function, and nuclear factor-E2-related factor 2 protein-coding gene. This indole involves the effects of TRAIL signaling through the induction of cell death receptors and synergizes with standard chemotherapeutic agents by inhibiting the expression of Pglycoprotein (P-GP). In in vivo studies, Indole- 3 carbinol was found to be a well-recognized chemopreventive agent to minimize the effects of hormone-dependent cancers, such as breast and cervical cancers.[64] These effects aggravate its skill to induce apoptosis, slow down DNA-carcinogen adduct formation, repress free radical production, kindle 2-hydroxylation of

estradiol, and inhibit tissue invasion and angiogenesis. Early clinical trials in women have shown that Indole3 carbinol is a notable agent against breast and cervical cancers.[64]

Table 4: Molecular targets of different plants having tumour suppressor potential in breast cancer.[4]

Sr. No	Molecular target	Ayurveda name	Botanical name	Relevant Ayurvedic classical uses	Activity on breast cancer	Classical Ayurvedic reference	Reference molecular target
1.		*Rajika*	Brassica juncea (L.) Czern.	*Sotha* (suppressor of Inflammation)	Multiple anti-tumour effect	GN. 2.32.123	Mazumder et al., 2016
2.		*Atasi*	*Linium usitasium* L.	*Sotha* (suppressor of Inflammation)	Reduces cellular proliferation	CS.CI.25.51	Roy et al., 2017
3.	↓NF-κB, ↓AP-1, ↓Egr-1; ↓COX-2, ↓LOX, ↓iNOS, ↓MMP-9, uPA, ↓TNF,	*Haidra*	*Curcuma longa*L.	*Granthi* (cyst)	Repress carcinogenesis of the breast	VM.57.97	Giordano and Tommonaro, 2019
4.	↓chemokines; ↓cyclin D1; ↓EGFR, ↓HER2	*Draksha*	*Vitis vinifera* L.	*Granthi* (cyst)	Cell-cycle arrest	SS.CI.18.9	Aggarwal et al., 2004
5.		*Adraka*	*Zingiber officinale* Roscoe	*Sotha* (suppressor of inflammation)	Suppresses breast cancer growth	CS.CI.12.49	Agents and Lechner, 2019
6.		*Aswagandha*	*Withaniasomnifera* (L.)	*Granthi* (cyst)	Induces cell death	CS.CI.21.123	Dutta et al., 2019
7.		*Gunja*	Abrus precatorius L.	*Sopha* (oedema)	Reduced cell viability	BP.CI.44.47	Shafi and Sateesh, 2013

Aromatase-inhibitors for breast cancer

less estrogen stops the growth of hormone-receptor-positive breast cancer cells.[61] Aromatise inhibitors can interfere with estrogen binding sites to encourage the growth of ER-positive breast cancers.[61] Plant species depicted in Table 5 may inhibit aromatase using a microsomal assay.

Table 5: Molecular targets of different plants used to inhibit Aromatase enzyme in Breast cancer.[4]

Sr. No	Molecular target	Ayurveda name	Botanical name	Relevant Ayurvedic classical uses	Activity on breast cancer	Classical Ayurvedic reference	Molecular target reference
1.							Das and Vinayak, 2014
2.	GLUT-1						Das and Vinayak, 2014
3.		Haridra Dalchini Draksha	Curcuma longa L. Cinnamomum zeylanicum Blume Vitis vinifera L.	Visarpa (erysipelas) Sopha (odema) Granthi (cyst)	Modulate glycolytic enzymes	SS.CI.11.9 CS.CI.23.205 VD.13.18	Deluc & Jaiswal, 2014

GLUT-1 inhibitors

The medicinal plants depicted in Table 6 are known to modulate glycolytic enzymes, cancer cells that use glycolysis to meet their energy needs are highly dependent on the glycolytic pathway and prefer glucose fermentation over mitochondrial oxidation, even under aerobic conditions.[65]

Table 6: Molecular targets of different plants used to inhibit GLUT-1 in Breast cancer.[4]

Sr. No	Molecular target	Ayurveda name	Botanical name	Relevant Ayurvedic classical use	Activity on breast cancer	Classical Ayurvedic Reference	Molecular target Reference
1	Aromatase	Draksha	Vitis vinifera L.	Sula (pain)	Reduces tumour weight	VD.13.18	Wahner-roedler et al., 2016
2		Shatavari	Asparagus officinalis L.	Stanyajanana (galactagogue)		YR.P.427	
3		Rakta sarshapa	Brassica Compestris L.	Gandamala (lymphatic disorder)		VM.41.47	
4		Rajika Jambira	Brassica juncea (L.) Czern.	Gandamala (lymphatic disorder)		VM.41.47	
5		Haridra	Citrus limon L.	Sula (pain)	Reduces growth-stimulatory effects of estrogens	VM.65.14	
6		Yastimadhu Kadali	Curcuma longaL.	lymphatic disorder		VM.42.14	Reuter S et al., 2010
7		Dadima	Glycyrrhiza glabra L Musa paradisiaca var.	Gynaecological diseases		BP.CI.68.13 RM.31.3; G.	
8		Adraka	sapientum (L.) Kuntze. L	Gynaecological diseases		Ni.6.1.69 SB.4.811; BP.	
9			Punica granatum L.	Swollen lymph nodes		CI.51.26	
10			Zingiber officinale Roscoe	Swollen lymph nodes		BS.Slipada.11	

Lectin containing plants

Evidence indicates that selective overexpression and activation of epidermal growth factor receptors and Src regulates oncogenesis in triple-negative breast cancer.[66] AnnexinA2 (AnxA2) membrane deposition plays a critical role in epidermal growth factor in tumour invasion and metastasis in breast cancer cells.[67] The medicinal plants containing lectin are depicted in Table7.

Table 7: Molecular targets of different plants used for Lectin in Breast cancer[4]

Sr. No	Molecular target	Ayurveda name	Botanical name	Relevant Ayurvedic classical uses	Activity on breast cancer	Classical Ayurvedic reference	Reference molecular target
1.	AnxA2	Neem	Azdiracta indica A.Juss.	Galacto-depurant	Decreases the expression of anti- apoptotic Bcl-2 family proteins	CS.CI.30.259 VM.65.14	David et al., 2016
2. 3.		Jambira	Citrus limon (L.) Vitis	Sula (pain)		VD.13.18	Dolan et al., 2010
4.		Draksha	vinifera L.	Sula (pain)		BP.Haritakyadi.119	Patel et al., 2012
5.		Saunf	FoeniculumvulgareMill.	Sula (pain)		CS.CI.21.67	Timoshenko et al., 1999
6.		Amalaki	Emblicaofficinalis Gaertn.	Visarpa (erysipelas)		GN.6.7.9	Govind, 2014
7.		Tulasi	Ocimum basilicum L	Sula (pain)		SS.CI.19.53– 54	Adavirao and Dr., 2018
		Eranda	Ricinus communis L.	Gandamala (lymphatic disorder)			Adavirao and Dr., 2018
8.		Tambula	Piper betel L.	Gandamala (lymphatic disorder)		BP.CI.45.12	Gundala and Aneja, 2014.
9.		Kumari	Aloe vera (L.) Burm.f.	Stana vyatha (mastitis)		GN.6.8.23	Ozsoy et al., 2012
10.		Krishna sarshapa	Brassica juncea (L.) Czern.	Gandamala (lymphatic disorder)		GN.4.2.39	Salgar et al., 2018
11.		Kupilu	Strychnos nux-vomica L.	Sula (pain)		SB.4.101	Salgar et al., 2018

FUTURE DIRECTIONS IN AYURVEDIC MEDICINE FOR BREAST CANCER

Medicines having combinations of metals/minerals and herbs have an edge over herbal and polyherbal medicines being fast acting in low doses and having a better shelf life.[68] These include heavy metals such as mercury, lead, arsenic, and poisonous herbs which are included under the Schedule-E1 of the Drug and Cosmetic Act of 1940. Nanometals are also used in these formulations which include gold[69], silver[70], arsenic[71] and others. These have been found to exert an effect on cancer through different mechanisms. There seem to be substantial similarities between Ayurvedic nano bhasmas and green nanotechnology using scientifically verifiable modern tools (Chanda N et al., 2011) Ayurvedic bhasma is nothing buttraditionally synthesized nano-metal particle.[72]

The practice of integrative medicine by combining Ayurveda and modern medicine needs to be implemented and scientifically validated. It is urgently needed to support various theories used in these dosage-forms with source identification, standardization of process, quality control measures, standardization, and increased clinical studies to make it universally reliable and relevant as a medical modality. The preclinical in vitro and in vivo investigations in breast tumour bearing mice demonstrated that the nano-Ayurvedic bhasmas are safe and show excellent efficacy in the management of human breast cancer in a dose-dependent fashion.[69] Several researches have confirmed the fact that the phytochemicals used in Ayurvedic nano bhasma preparation are indeed electronrich antioxidants and that the interaction of Nano bhasmas precursors with phytochemicallyharnessed electrons produced herb/ phytochemicals-encapsulated, well- defined, nanoparticles. Combinations of herbs and nano ayurvedic bhasma that are effective on initiation, proliferation, and metastasis of tumour cells can prove to be a safe, cost-effective futuristic remedy for treating breast cancer.

Table 8: Molecular targets of different ayurvedic nano bhasmas used for Breast Cancer.[4]

Sr. No	Molecular targets	Ayurveda name	Chemical composition	Clinical condition usage	Activity on breast cancer	Classical Ayurvedic reference	Reference Molecular target
1.		*Sankhia (White arsenic)*	Arsenic trioxide	*Arbuda* (cancer), *Sotha* (inflammation) *Gulma* (tumour)	Induces apoptosis, Prevents tumour growth	RT.11.138–144	Ruhila et al., 2018
2.		*Hartala bhasma*	Arsenic trisulphide	*Visarpa* (erysipelas)	Induces apoptosis, prevents tumour growth	RT.11.64	Ruhila et al., 2018
3.		*Kajjali*	Black sulphide of mercury	*Gandamala* (lymphatic disorder) *Gulma* (tumour)	Induces apoptosis, prevents tumour growth	RT.6.123 R.T.6.212	Ruhila et al., 2018
4.		*Rasasindura*	Red sulphide of mercury	*Sopha* (oedema); *Visarpa* (erysipelas), *Vrana* (wound) *Arbuda* (malignant cancer)	Higher mitochondrial ROS level	R.T.6.220–221 RT.15.75	Ruhila et al., 2018
5.		*Swarna bhasma*	Gold nano particles	*Rasayana* (immuno modulator) *Stanya vardhaka* (lactogenic) *Sotha* (oedema)	High degree of penetration behaviour	RT.15.71- RT.15.106 RT.15.114	Khoobchandani et al., 2020
6.		*Lauha bhasma*	Iron oxide	*Rasayana* (immuno modulator) *Gandamala* (lymphatic disorder)	Induce T-cell mediated tumour suppression in breast cancer	RT.20.87–99	Soetaert et al., 2020
7. 8.		*Tamra bhasma*	Copper oxide	*Gulma* (tumour), *Sula* (pain), *Vrana* (wound)	Induce apoptosis in breast cancer cells	RT.17.69 RT.17.89	Shafagh, et al., 2015
9.		*Rajata bhasma*	Silver complexes	*Rasayana* (immuno modulation) *Sopha* (oedema)	Biogenic anti cancerous agent	RT.16.60–75	Arjunan et al., 2016
10.		*Vanga bhasma*	Tin oxide	*Gulma* (tumour), *Sula* (pain) *Vrana* (wound)	Induce cell viability reduction, lactate dehydrogenase leakage, cell cycle arrest and low mitochondrial membrane potential	RT.18.39–40	Ahamed et al., 2018
11.		*Swarna gairika*	Silicate of Alumina and oxide of Iron	*Visarpa* (erysipelas)	Increases cell velocity and nanoparticles uptake	RT.23.147	Reczyńska et al., 2020
12.		*Sankha bhasma*	Calcium carbonate	*Arbuda* (malignant tumour) *Vrana* (wound) *Gulma* (tumour) *Sula* (pain)	Tumor-suppression capability	RT.12.22–29	Wei et al., 2019
13.		*Navasadar*	Ammonium Chloride	*Sopha* (oedema)	Increases mitochondrial cytochrome C release	RT.16.109	Guo et al., 2016
14.		*Mandura bhasma*	Iron oxide	*Sopha* (oedema)	Induces T-cell mediated tumour suppression	RT.21.136	Soetaert et al., 2020
15.		*Swarna makshika bhasma*	Copper Sulphide	*Sopha* (oedema)	Enhances immunotherapy	RT.21.246	Chen et al., 2019
16.		*Praval bhasma*	Calcium carbonate	*Vrana* (wound)	Tumor-suppression capability	RT.23.149	Wei et al., 2019
17.		*Kasisa bhasma*	Ferrous sulfate	Visarpa (erysipelas)	Corrects iron deficiency anemia (IDA) in breast cancer patients	RT.23.149	Ferrari et al., 2012
18.		*Kaprada bhasma*	Calcium carbonate	*Vrana* (wound)	Tumor-suppression capability	RT.12.97	Wei et al., 2019
19.		*Sphatika bhasma*	Aluminium Sulphate/ Potassium Sulphate	*Vrana* (wound), *Visarpa* (erysipelas)	Immunogenic, Suppress tumour growth	RT. 11.184	Garg et al., 2018
20.		*Yavakshara*	Carbonate of potash	Gulma (tumour) *Sula* (pain) *Sotha* (oedema)	Enhances the anti-tumour effect	RT.13.12 RT.13.10 RT.13.14	Frajese et al., 2016
21.		*Sarjikshara*	potassium carbonate	*Gulma* (tumour) *Vrana* (wound)	Enhances the anti-tumour effect	RT.13.49	Frajese et al., 2016
22.		*Apamarga kshara*	Achyranthine	*Arbuda* (malignant tumors), *Gulma* (tumour)	Enhances the anti-tumour effect	RT.14.66	Frajese et al., 2016
23.		*Palash kshara*	sodium, potassium, chloride, and carbonate ions	*Arbuda* (Malignant tumors)	Enhances the anti-tumour effect	RT.14.104	Frajese et al., 2016

Abbreviations of Classical Ayurvedic references: AH: Ashtanga hridaya; BP: Bhavprakash; BS: Bangasena; CD: Chakradutta; CI:Chikistha sthana; CS: Charak Samhita; GN: Gada

nigraha; Ka: Kalpa sthana; RM: Rasa marttanda; Sa:Sharira sthana; SB:Siddha bheshjya mannimala; SG:Sharangdhar Samhita; Si:Siddhi sthana; SS:Susruta Samhita; Su:Sutra sthana; VD:Vaidya manorama; VJ:Vaidya jivana; VM:Vrinda madhav;MN:Madhav Nidan.[32]

CONCEPT OF PANCHKARMA IN TREATMENT OF BREAST CANCER

The words Panchakarma mean "five actions" or "five processes". Panchakarma is a complete detoxification program that utilizes food, herbs, oils, simulative therapies to eliminate morbid or toxic matter from the elimination channels of the body, followed by rejuvenating therapies that restore balance and health. Cleansing the cellular microenvironment allows the natural healing mechanisms of the body to restore functional balance to the physiology of each cell. a natural purification treatment can successfully eliminate environmentally toxic substances such as polychlorinated biphenyl (PCB‟s) and pesticide from the body, without damaging side effects. A study of institute of Science, Technology and public policy at Maharshi University of Management in Fairfield, lova in collaboration with a special laboratory at Colorado University demonstrated that classical Panchakarma treatment eliminate up to 50% of detectable toxins in the blood.[73]

AIM OF PANCHKARMA TREATMENT

Aim of Panchakarma treatment is to cleanse & detoxify body, increase immunity & thus to restore health. In many Cancer patients, it helps to reduce sufferings, minimize side-effects of Chemotherapy & Radiotherapy. It also helps to prevent recurrence of Cancer. All disease occurs due to suppression and forceful expulsion of natural urges. Panchakarma is the best treatment for the diseases caused by suppression of natural urges.[74]

TREATMENT PROTOCOL OF CANCER

Natural therapies such as Ayurveda, make use of plant-derived products in cancer treatment, which may reduce adverse side effects. This traditional Indian medicine of plant drugs has been successfully used in cancer treatment through various Panchakarma procedure from ancient time.[75]

The other type of curative therapy is called samana chikitsa, which pacifies dosha and gradually relieves the disease. However, this treatment is prescribed only to weaker patients for whom sodhana chikitsa is contraindicated. In Rasayana prayoga (immunotherapy), certain poisonous plants, mercury like metals and animal products were rendered non-toxic and harmless by the use of alchemy and are used as rejuvenating drugs. Other methods of

treatment include, dhatwagni chikitsa (correction of metabolic defects), vyadhipratyanika chikitsa (specific anti-cancerous drugs) and lakshanika chikitsa (symptomatic treatment).[76]

PRE – PROCEDURES (PURVAKARMA)

Deepana (digestion of Ama), Pachana (separation of Dosha from Dhatu), Snehan and Swedana the Dosha should be expelled from nearest route at proper time according to the strength of Roga and Rogi.[77]

SNEHANA (Internal and external oleation) Antioxidant properties, it reduces ROS in the body.

SWEDANA is sudation or sweating and is given every day, immediately following the snehana.

Swedana liquifies the toxins and increases the cellular metabolic activities.

MAIN PROCEDURE (PRADHANA KARMA)

Panchakarma is activating the bodies selfhealing ability but also calm the Doshas and Gunas including removing of aggravated Doshas and toxins from the body. If a patient underwent chemotherapy and radiotherapy it is beneficial for both body and mind. After Panchakarma therapy Rasayana should be given prescribed along with immune-modulators and antioxidants (Withania, Ginger, Podophyllum hexandra, Amla, Guduchi, Curcumin etc.).[78,79,80]

Pradhana Karma (Main procedures)

Inducing vomiting *(Vamana)*

Appropriate Condition :- Kapha dominating symptoms in Cancer. Inducing Purgation *(Virechana).*

Appropriate Condition :- Pitta dominating symptoms in Cancer. Medicated enema *(Basti).*

Appropriate Condition :- Vata dominating symptoms in Cancer. Nasal Medication to eliminate the Doshas *(Nasya).*

Appropriate Condition :- Kapha & Vata dominating symptoms in Cancer. Blood letting *(Raktamokshana).*

Appropriate Condition :- Symptoms of vitiated Pitta & Rakta in Cancer.

Vamana Karma and its scientific explanation

The principle of Vamana drug taken orally is absorbed from the stomach into circulatory system, where from it is circulated to all over body. On reaching at the site if lesion (Dosha Sanghata), which is at the cellular level, it breaks the nexus of Dosha and brings back the toxic substance thus released into the stomach, where from they are expelled out the body by the action of Vamana.

The smaller molecules thus formed can be driven out of the cell due the normal function of the cell or by the action of drug thus the cell is freed from the harmful substance leading to the cure of the degeneration. It will increase the permeability of the capillaries of the stomach, which in the beginning facilitate the absorption of the active principles of the drug and later on facilitates the excretion of the toxins and metabolites into the stomach where from they are thrown out of the body by the process of the Vamana.[81]

Virechan karma and its scientific explanation

It is the process of purgation via anal route. that Ayurvedic Shodhana are mild irritant to the stomach and the intestinal mucosa respectively, to cause inflammation. Due to this the permeability of the membrane changes and those substance come out due to changed permeability. This medically produced mild inflammation facilitates quick absorption of the active principles (Virya) of the drug in initial stage to be excreted out through the mucosa of the gut. Exudation is increased passage of protein rich fluid through the vessel wall, in the intestinal tissue. The advantages result of fluid increases is dilution of toxins.

Nitric Oxide (NO) also involved in stimulation of intestinal secretion via prostaglandin and cyclic-GMP- dependent mechanism, in addition, NO may inhibit segmenting contraction in the colon, promoting laxation. A variety of laxatives both osmotic and stimulant have been found increase the activity of NO synthesis and to increase the biosynthesis of PAF in the gut.[82]

Basti Karma and its scientific explanation It not only cure Vatika disorders but also Samsarga and Sannipata condition of Dosha, Kaphajaand Pittaja disorder, Shakhagata and Koshthagata Roga by combination of different types of Basti Dravya.[83]

As per the contemporary view, in last part of intestine, digestion occurs through bacterial action and no enzymes are secreted by colon. These beneficial bacteria or micro flora mainly resides in colon synthesize vitamin K, B and convert indigestible or partially digested saccharides (e.g.

Lactose) into short chain fatty.[84]

Colon normally absorbs 12 liters/day but is capable of absorbing almost 6 liters/day. Various nutritive end products are absorbed from the mucosa of gastrointestinal tract mainly through the Na^+ channels and other ion channels. The absorptive capacity of the mucosa of the large intestine is great, Na^+ is actively transported out of the colon, and water follows the osmotic gradient thus generated. Although the rectum is not a usual site for absorption of indigested nutrients, drugs introduced by rectum may be absorbed there. Thus, drugs introduced by this route may have systemic effects as well as local effects. Drugs absorbed into external hemorrhoidal veins (above 50%) by passes liver but not that absorbed into internal hemorrhoidal veins. Colon mucosa under the effect of medication can be made to absorb the unusual substances also.[85]

Nasya karma and its scientific explanation

The drug administrated through nose as Nasya reaches the brain and eliminates only the morbid Dosha responsible for producing disease because nose is the gateway of head.[86] Nasya not only beneficial for Upper body part diseases but also for some systemic disease such as Cancer, Kampvata Pumsvana etc.[87] The mode of action of the drug is a most complex phenomenon and at times it becomes difficult to pin point the therapeutic action in a very precise and scientific manner. Some of the hypothetical views by research workers are mentioned as (i) through the general and specific blood circulation, (ii) through the lymphatic channels including CSF (iii) through the neuroendocrinal and Neurovascular stimulations. These lipid soluble substances also gain in to the lymphoid tissue. Thus, a rapid circulation through the lymphatic channels is a positive phenomenon, on other hand, the extended arachnoid sleeve from the brain to the absorption of drug material directly to nose. It has been observed that the experimental administrations of the contraceptive hormones in the animals were found to be of higher concentration in the CSF and their concentration was equal with the intravenous infusion of the same drug.

The Olfactory nerve functions by mean of Chemoreception. The chemical characteristics of the practical that has reached to the nose will be identified by nerve which carries the stimuli to the Olfactory bulbs. Further, the massage will be carried out to the highest centres probably involving the hippo campus, limbic system, hypothalamus etc.

Nasya Karma is also said to influence upon the neuro vascular functioning which may help in

better drug availability to the brain.[88]

POST PROCEDURE (PASCHAT KARMA)

Immediately after Panchakarma, Digestion Power (Jatharagni) becomes weak. To improve it slowly, the patient should follow special diet regime i.e. Samsarjana Krama. It lasts for 3 to 7 days. It contains-Thin rice gruel (Peya), Thick rice gruel (Vilepi), Plain bean soup (Akruta Yusha), Medicated bean soup (Kruta Yusha), Plain non-veg soup (Akruta Mansarasa), Medicated non-veg soup (Kruta Mansarasa). The general rule is that the aggravated Doshas should be eliminated by the nearer path in the body. Thus, a specific type of Panchakarma has to be done in specific type of Cancer under the guidance of experienced physician.[89]

CYSTOGRIT DIAMOND

DESCRIPTION IN CLASSICAL TEXTS

Cystogrit Diamond was formulated using heerak bhasma as an important ingredient. It makes this medicine very effective against various tumors. Bhava prakasha mentiones Kanchnar under Guduchyadi varga. This drug has astringent taste and light and dry qualities. It has katu vipaka. It is cold in potency and pacifies Kapha and pitta doshas. By its prabhav, it is Gandamala nashana, curing thyroid disorders. This drug has the ability to cure tumors located at various parts of the body.

Bhava prakasha has mentioned Haridra under Hareetakyadi Varga. It has pungent and bitter tastes. It pocess quality of dryness and is hot in potency. It pacifies kapha pitta doshas. It has anti-inflammatory action. It can cure blood related diseases. It has wound healing potential.

Prepared with purified realgar, purified mercury and purified Sulphur mixed with aloe vera juice and incinerated, shila sindoor, Muktashukti pishti useful in gastritis and cancer . Moti pishti can alleviate mano doshas. It is prepared by taking mukta bhasma and triturate with rosewater. Tamra bhasma may cure anemia, kapha-pitta roga and cancer.Heerak bhasma pacifies all three doshas. It is effective in respiratory ailments.

SCIENTIFIC EVIDENCE OF CYSTOGRIT DIAMOND

In a research study conducted by Patanjali Research Foundation, the therapeutic potential of Cystogrit Diamond against leukemia was deciphered. The study determined the potential of Cystogrit Diamond in inducing differentiation therapy in leukemia cells. The commercially available leukemia-derived immortalized cell lines were utilized to study the anti-leukemic

effects of Cystogrit Diamond. Treatment of Cystogrit Diamond in both the cell lines, HL60 and K562 induced drastic nuclear morphological changes indicating the induction of differentiation in the leukemic cell lines. Giemsa staining demonstrates modulations in nuclear shape and segmentation of both cell line models used in the study, K562 and HL60 cells when treated with Cystogrit Diamond. Surface membrane proteins, known as cluster of differentiation (CD markers) help biomarkers in assessing differentiation in leukemia cells. In HL60 cells, Divya Cystogrit showed a significant rise of 11% CD11b and CD14 positive cells. Interestingly, K562 showed a much higher rise compared to HL60. CD11b positive cells increased by 16% whereas CD41 positive cells increased by ~ 33%. In addition, Cystogrit Diamond also modulates the transcription factors and associated genes that regulate differentiation in haematopoietic cells. Cystogrit Diamond treatment in HL60 and K562 induced changes in the gene expression levels of CD61, NFE2, CD41 and CCAAT-enhancer-binding proteins a (C/EBPa). Collectively, this study has identified therapeutic potential in Cystogrit Diamond for the treatment of leukemia. For phytochemical study, Reverse Phase Ultra High Performance Liquid Chromatography (RP. UHPLC) was developed. The study confirms the presence of 5-hydroxy methyl furfural (5-HMF), vanilic acid, ferulic acid, at 270 nm wavelength and bisdemethoxy curcumin, demethoxy curcumin and curcumin analysis at 420 nm wavelength on comparison with the reference standard.

INGREDIENTS AND MEDICINAL USES OF CYSTOGRIT DIAMOND

INGREDIENT	**BOTANICAL NAME/ PREPRATION**	**PROPERTIES AND ACTION**	**USES**	**EACH TABLET CONTAINS**
Dry extract of :				
Kanchnar (Bk)	*Bauhinia varigata*	Galgand,Granthi RogHar	Cures thyroid disorder and tumors	301.72mg
Haldi (Bk)	*Curcuma longa*	Shothaghna Vishaghna	.Anti inflammatory . Anti toxic	51.72mg
FINE POWDER OF :				
Shila Sindoor	Classical Preparation	Aruchi Galgand Har	.Taste enhancing .Cures thyroid disorders	34.48mg
Muktashukti Pishti	Classical Preparation	Raktaj Gulma Har	.Cures abdominal swellings of rakta origin	68.97mg
Moti Pishti	Classical Preparation	Pittaj Vikar Har, Kshay Rog Har	.Cures diseasescaused by pitta dosha .Cures phthisis	17.24mg

Tamra Bhasma	Classical Preparation	Arbud Har, Gulma Har	.Anticancer .Cures abdominal swellings	17.24mg
Heerak Bhasma	Classical Preparation	Rasayan, Karkat Rog Har	. Rejuvenating . Anti Cancer	8.62mg

CASE STUDY

In a recent case study presented in Ayush Cancer Conclave, Considering breast cancer as Sthana Arbuda (place of tumour) & since it is a Kapha Sthana, first classical Vamana (therapeutic vomiting) therapy was started. After 6 months classical Virechana was done. Then classical Vamana & classical Virechana (therapeutic purgation) procedures were repeated alternatively once in 6 months for 3 years. Totally three procedures of Vamana & three Virechana were done. Along with Urdhwa & Adhah Shodhana (internal and external clensing process), patient was given Paneeya Kshara (liquefied alkaline ash) & other Kaphahara Ahara &Grantihara Yoga. Periodically, Mammogram & ultrasound scan of breast was done to assess the size of the breast tumour. To our surprising the breast tumour size constantly reduced & there was no spread of the disease (no metastases). Detailed treatment protocols, Shamana Aoushadhi (pacifying medicines) were given.

After three years of treatment, with repeated classical Vamana Karma, classical Virechana Karma, Paneeya Kshara & other Shamana Aushadhi (pacifying medicines) the breast tumour which was malignant & 3.85 × 1.24 × 3.52cm before the treatment, it was reduced to 0.5cm and turned into benign cyst and also the metastatic right axillary lymph node which was measuring 2.74 × 1.45cm before treatment was reduced to 8 mm. Ayurvedic treatment in this case was very effective in reducing the size of the tumour & also arrested the spread of the disease/metastasis. Before treatment BIRADS category was VI i.e. known malignant, which after 3 years of treatment, became BIRADS category II i.e. benign findings. The results were effective & encouraging. During the course of treatment patient didn't experienced any untoward reaction or side effect, the treatment was 100% success without even any single short term or long term side effect.

Above mentioned case proved that Ayurveda has got definitely major role in the management of breast cancer, but we have to understand the breast cancer & all other modern investigation reports on the basic concepts of Ayurveda like Dosha (functional enrgy of body), Dhatu (body tissues), Mala (waste product o body), Agni (balanced digestion), Ama (poor digestion), Strotas (macro and micro channels of body) etc. After evaluation of breast cancer classically, then we

should treat it with some specific Ayurveda line of treatment (Chikitsa Sutra) for the success. Breast cancer can not be managed merely with administration of so called some anti cancerous herbal drugs.[90]

Management of cancer patients with Ayurveda[91]

- Nidanaparivarjana i.e. avoidance of causative factors of the disease
- Shamanachikitsa (treatment using Ayurvedic medicines orally)
- Shodhanachikitsa (detoxification through Panchakarma therapy)
- Rasayanachikitsa (immunotherapy, rejuvenation or Kayakalpa)
- Diet & life style management
- Satvavajaya (counseling)
- Daivavyapashrayachikitsa (divine therapy), Yoga & Pranayama are also suggested asper the need and condition of the patient.

Nidanaparivarjana

- Avoidance of causative factors i.e both Aaharaja and Viharajahetu is called as Nidanaparivarjana.
- Ayurveda advocates to live according our constitution, daily and seasonal rhythm – to prevent or restore the imbalance of Doshas and Dhatus as well as enough exercises.
- Practice meditation and Yoga for mental and physical relaxation, listen to harmonious music is healing and calming the mind. Try to have more Sattvicfoods (vegetarian andless spicy), to balance both body and mind, respectively Doshas and Gunas. Sattvic foods consist of fresh, energizing foods as fresh fruits and (leafy) vegetables, milk, cereals, pure fruit juices, butter and fresh cheese, fresh nuts, seeds, sprouts, honey andherbal teas. No snacks or fast food and ready-to-eat meals. Avoid microwave ovens, limit meat consumption, especially red meat.
- Ayurveda has always turned to nature for inspiration to practice medicine and wisely uses natural resources.[91]

Shodhana and Shamana- Shodhana Chikita

Purification of body by Vamana, Virechana, Basti, Raktamokshana, Nasya and Karnpooran. Aim of Panchakarma treatment is to cleanse & detoxify body, increase immunity & thus to restore health. In many Cancer patients, it helps to reduce sufferings, minimize side-effects of Chemotherapy & Radiotherapy. It also helps to prevent recurrence of Cancer.[91]

Treatment (Chikitsa) of Cancer

- Mitigating all the three doshas (Tridosh – Shamak) according to dominance of doshas.
- Dhatvagni – Deepan: - Improving Metabolic activities (dhatvagni) especially Rasa – Rakta and Mansa dhatvagni.
- Controlling Dhatugataavastha :- (The nature of doshas of embedding in deeper & deeper tissues and vitiating them)
- Prevention of DhatupakaAvastha:- By Pittashamaka&Raktaprasadaka treatment.
- Rejuvenation to affected organ (Rasayana):- Depending upon strength of the patientand vitiated doshas.
- Panchakarma (ShodhanaChikitsa) eliminates the vitiated doshas from the body.

Shamana Chikitsa

To subside the symptoms of elevated Doshas with the help of drugs is called as Shamana. Many Ayurvedic plants and minerals are used for the treatment of Cancer. Extensive researches during the last 30 years have revealed much about the biology of cancer. Drugs used to treat most cancers are those that can block cell signaling, including growth factor signaling (e.g. epidermal growth factor); prostaglandin production (e.g. COX-2); inflammation (e.g., inflammatory cytokines: NF-kappaB, TNF, IL-1, IL-6, chemokines); drug resistance gene products (e.g., multi-drug resistance); cell cycle proteins (e.g., cyclinD1 and cyclin E); angiogenesis (e.g., vascular endothelial growth factor); invasion (e.g., matrix metalloproteinases); antiapoptosis (e.g., bcl-2, bcl-X(L), XIAP, survivin, FLIP); and cellular proliferation (e.g., cmyc, AP-1, growth factors). Numerous reports have suggested that Ayurvedic plants and their components mediate their effects by modulating several of these recently identified therapeutic targets.[92] shallaki has shown some promising effects in management of pain.[93]

Most of the synthetic chemotherapeutic agents available today are immunosuppressants, cytotoxic, and exert variety of side effects that are particularly evident in cancer chemotherapy. Botanical based immunomodulators are often employed as supportive or adjuvant therapy to overcome the undesired effects of cytotoxic chemotherapeutic agents and to restore normal health. Some drugs which are anti-cancerous are Haridra, Amlaki, Shatavari, Kalmegh, guduchi, Bhallataka, Ashwagandha, guggulu etc.

Rasayana

Rasayana is an exclusive concept stated in Ayurveda. Rasayana is one among the eight clinical specialties of Classical Ayurveda (Ashtanga Ayurveda). It is not only a drug therapy but is a specialized procedure practiced in the form of rejuvenative recipes, dietary regimen and special health-promoting conduct and behavior (AcharaRasayana). Rasayana comprehends all the modalities of Health Care i.e., Preventive, Curative, Eliminative, Restorative, Behavioral, Pharmaceutical, Dietetic and so on. Mode of action of this therapy is specific in increasing the life span, significant improvement in quality of life and prevention of disease.

Benefits of Rasayana in cancer patients.

- Easy Oral mode of drug administration.
- Reduces disease symptoms.
- Significantly improves patient's Quality of life.
- Helps in Tumor regression.
- Increases survival period in all types of cancer patients.
- Prevents the progression of disease.
- Significantly reduces the risk of relapse in cancer survivors.
- Shows very significant action in reducing the side effects of Chemotherapy/ Radiotherapy.
- Neuro-endocrine theory also known as Programmed cell death theory, postulates that all somatic cells have a built in biological clock, or a genetically controlled life span, after which they would die, no matter how favorable circumstances are. Immunological theory states that mutated cells stimulate immunological reactions within the organism and these reactions themselves degrade and eventually destroy the organism. Evidence from these theories of ageing supports the potential role of Rasayana, as it shows the multiple actions on different systems of the body by modulating the Psycho- Neuroendocrine-Immune systems.[94,95]

Diet & life style management

In case of a loss of appetite, eat a number of small meals instead of three large meals. Drink a little bit more before and after meals. Avoid cold foods as they suppress digestive fire. If solid foods cause problems, replace them with nutritious soups. Use herbs to boost the immune system. In case of nausea use ginger. Choose predominantly plant based diets rich in fruits and vegetables .Restrict the intake of redmeat (beef, pork etc.) and preserved meat. Eat satvik and

biologically fresh fruits and vegetables.

- Say no to snacks and fast food. Reduce the use of microwave oven for cooking.[96]
- Satvavajaya (couselling):

Stress and anxiety go hand in hand in cancer patients. Typically, people approach problems in one of two ways

- Actively working on them.
- Avoiding them.

In general, active coping works better and is healthier.Active ways to manage stress[97]

- Take break from news about pandemic on social media.
- Stay in touch with people who can provide emotional and other support.
- Take time to do relaxing activities you enjoy like cooking, yoga etc.
- Focus on nutritious diet

Daivavyapashrayachikitsa (divine therapy), Yoga & Pranayama

Yoga is basically preventive life sciences and helping the patients understand their condition finding the root causes of the problem and creating a healthy opportunity for them to change themselves. The chronic diseases are spreading very fast as epidemic putting a break for this epidemic is today's need. This can be done by health promotion through healthy diet and of simple, cheap and cost effective measures, proper management and care of the patient. Yoga, Meditation and Pranayam are century old, time tested processes, these are known to relax mind and energize the body.

Meditation- Meditation can be useful to some people in dealing with side effects of treatment and in overcoming the sense of loss of control and to promote health and reduce the risk of recurrence.[98] Sudarshankriya and Pranayam are highlighted to induce relaxation, increase antioxidant defense and NK cell in the body. Sudarshankriya and Pranayam may have a preventive role against cancer.

Both may be effective as secondary preventive measures after curative treatment of cancer and in metastatic cancer, Sudarshankriya and Pranayam may delay progression of cancer improve survival and quality of life.[99]

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