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Oncoprotective Role of Ayurvedic Herbs and their Phytochemicals in Cancer Therapy

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ABSTRACT

Cancer is one of the most prevalent non-communicable diseases spreading drastically in developing and industrialized nations. It is one of the foremost causes of death across the globe and mortality due to cancer is increasing morality due to cancer is increasing because of limited available effective therapy. Cancer is characterized by uncontrolled growth of cells due to dysregulation of cell cycle and apoptosis. Recent advances in cancer therapy are burdened by drug-induced side effects due to non-selective targeting of normal tissues. Although natural products play a significant role in the development of most chemotherapeutic agents but very precise target-oriented therapy is still unavailable. Ayurveda, the ancient traditional Indian healing system describes 15000 medicinal plants for treating various ailments, out of which 7000 plants are currently being used. Ayurveda also describes varies types of medications for the treatment of cancer which are yet of be validated. Nowadays rigorous researches are underway to elucidate the role of Ayurvedic herbs and their contained phytochemicals in the management of cancer. This review provides some insights on the current research of anticancer herbs described in Ayurvedic contexts. Here we focus on how herbs and herbal formulations reported in Ayurveda can be used for the development of targeted cancer therapy. In short, the data presented in this review supports view of that herbs and herbal formulation as per ancient Indian healing system can be integrated with western medical system or be used synergistically towards the development of effective anticancer therapy.

Key Words: *Cancer, Ayureveda, herbs, Herbal formulations, Phytochemicals, therapy*

INTRODUCTION

Cancer has become the deadliest disease in 21st century according to World Health Organization. Each year more than 1.2 million new cases of invasive cancer are confirmed only in the U.S., and about 500,000 deaths are reported from the disease [1]. Nowadays it is evident that cancer is related to changes in the environment, dietary and erratic irregular lifestyle of individual beings. Over the year's lung, esophagal, prostate, stomach, oral and pharyngeal cancers are increasingly becoming predominant in males whereas cancers of cervix and breast are common in females.

Modern science has been very keen in understanding the cause and treatment of cancer but the exact etiology of disease and an effective management of cancer in general are remains to be an unresolved mystery to the researchers. Although scientists have developed many cancer treatment strategies like surgery, chemotherapy and radiotherapy but these treatment strategies are still believed to be beyond the reach of common people due their excessive cost. Besides that chemotherapy and radiotherapy employed in the treatment of cancer have

serious side effects leading to residual morbidity and relapses[2].

Ayurveda stands for "Science of Life" and is the world's oldest holistic healing system originated in Indian subcontinent. Ayurveda emphasizes the steadfast interconnectedness between the body, mind, and spirit and thus balancing the natural harmony of every individual. Ayurveda has successfully recognized and characterized several forms of cancers and mentioned numerous herbs and herbal formulations for the management of the conditions. If extensive research is done by using modern scientific methods on the herbs and herbal formulations listed in Ayurveda, very cheap and more effective medications can emerge very soon for patients If the herbs and herbal formulations described in Ayurveda evaluated with the modern scientific approach, cheap and effective remedies for the patients may come out very soon. The present chapter summarizes the available information regarding the treatment of various cancers using herbs and herbal formulations described in Ayurvedic texts with the intention of raising awareness and encourage integrative approach for development of effective target-oriented cancer management.

Ayurvedic concept of cancer

Ayurvedic concept of cancer stands on Tridosha theory. According to Ayurveda philosophy when there is a balance between Tri-doshas called Vata (air), Pitta (fire) and Kapha (water), health exists. Ayurveda does not contemplate cancer as a single disease or some group of diseases. Instead, Ayurveda describes that all diseases arise from severe, systemic imbalances and malfunctions of the three Doshas. Specific diseases like cancer develop from reciprocity between abnormal Doshas and weakened Dhatus [3, 4]. Cancer results when abnormal interactions between *Prakriti* (genotype) and environmental factors destroy the *Doshas* and decrease immunity. Interaction between impair *Doshas* and weak tissues (*Dhatus*) manifests as cancers of specific organs.

The earliest and foremost records of malignancy are cited in *Atharva Veda* (2200 B.C. Where the disease was possibly identified as apachi or apachit, which refers to the current awareness of dif ferent types of swelling of the lymph nodes.

Two most popular Ayurvedic classics *Charaka* and *Sushruta* [5] samhitas, states cancer as inflammatory or non-inflammatory swelling and termed them as either *Granthi* (minor neoplasm) or *Arbuda* (major neoplasm). In benign neoplasm (*Vataja*, *Pittaja* or *Kaphaja*), one or two of the three bodily systems are out of control but it is not too damaging to the body because the body as a whole is still trying to harmonize these dohas. Malignant tumours (*Tri- dosaja*) are considered very harmful because of the loss of mutual coordination among Dohas. As the mutual coordination is lost, thus the body and cannot avert tissue damage which results in a deadly morbid condition [5].

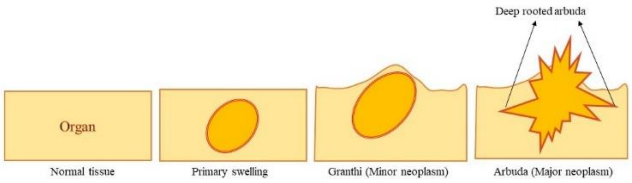

Figure 1 Formation of Granthi and Arbuda as described in classical texts of Ayurveda

Etiology

Sushruta states that the underlying origin of major neoplasm is the pathogens that affect all organs of the body. He termed the sixth layer of the skin as *'Rohini*,' (epithelium). Tumor results due to

pathogenic injuries to this layer in muscular tissues and blood vessels. Derangement of doshas caused by lifestyle errors, unhealthy foods, poor hygiene and bad habits are the major causes of pathogenic injuries [5, 6]. Based on the genetic makeup of each individual, cancer in each person differs according to the person's exposure to pathogens, which make each of them to react in different ways to the exactly same diet.

Ayurveda also well documented the genetic cause for the manifestation of cancer. For example, *Sushruta* has described that defects in ovum (*sonita*) and sperm (*shukra*) are responsible for the pathogenesis of familial polyposis coli (*sahaja arsha*).

Pathogenesis and Pathophysiology of Cancer

According to Ayurveda disease in different persons cannot be named on its own because it is different between persons and depends on illness, physical sign and symptoms and remedies required [7]. Therefore, according to Ayurveda, cancer is picturised as a tridoshic disease that can to spread because of the interaction of vitiated vata, pitta, and kapha.

Concept of metastasis is different in Ayurveda from modern allopathy. As per Ayurveda, metastasis is caused by the active Vata dosha. Vata may be associated with anabolic growth process where kapha to the anabolic phase. Cancer develops due to the imbalance of metabolism where vata aggravates and kapha gets suppressed. Kapha being heavy and gross is responsible for the abnormal growth of the malignant tumour forming cells, and the tejas which is a core element of pitta enhances cancer cells' metabolic activity. The elevated pitta at the cellular level may bring micro inflammatory changes, which disturb the cellular components of agni called pilu agni and pithar agni. The pithar agni makes poorly formed tissue because of slow pilu agni. The malignant tissue has strong agni [8]. Ayurveda proposes six stages for the pathogenesis of cancer as described below:

1. *Sanchaya*: early stages of altered neoplastic localization.
2. *Prakopa*: primary growth trnasformation into metastatic tumours.
3. *Prasara*: Start of metastasis.
4. *Sthana samsraya*: completion of metastasis and start of secondary growth.
5. *Vyakti*: Exhibition of clinical signs and symptoms.
6. *Bheda*: Beginning of growth differentiation-based histopathology [9].

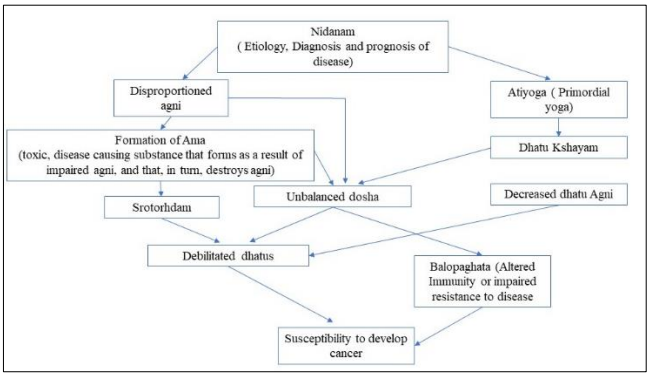

Figure 2 Ayurvedic overview of cancer pathophysiology

Ayurvedic terms used: Nidanam are root causes of ailments that includes inherited, dietary and lifestyle related causes. Digestive strength and metabolic rate of the body tissues are represented by Agni. Atiyoga means constant psychological and physical discomfort. Ama illustrates impurities and contaminants in the body. Kshayam means body tissue degeneration and degradation. Srotorhodam implies both physical and energetic

blockage(s) of body channels. Dosha imbalance indicates a vata, pitta and/or kapha imbalance. Dhatu agni is the dhatus metabolizing pace. Dhatus are tissues in the body. Balopaghata means impaired immunity, or impaired disease resistance.

Ayurvedic literatures on cancer treatment

Atreya and Dhanwantari, two most famous Ayurvedic physicians in ancient India reportedly had used herbal medicine for treating early stages of cancer and surgery in advance stages. During the Buddhist reign around 8th century, Ayurveda flourished in India. One of the renowned physicians during this era named Vagbhata composed two texts: *Astanga Hrdaya* [10] and *Astanga sangraha* [11] where he described new methods for cancer treatment. Later other classic ayurvedic text such as Chakradatta [12] composed by Chakrapani (10th century AD), the *Sarangadhara Samhita* [13] by Sarangadhara (14th century AD), the *Bhavaprakasha Samhita* [14] by Bhavamisra (15th century AD), the Satmya Darpan Samhita by Viswanath (16th century AD), the Vaisajya Ratnabali by Binoda Lala Sen Gupta (18th Century AD), the Rasatarangini by Sadananda Sharma (19th century AD), etc various treatment modalities for the cancers.

Ayurvedic Principle of Cancer Therapy

The basic goal of ayurvedic therapy is to find the cause of an illness. Thus, detoxification (shodhana therapy) plays in Ayurveda are a major part of the treatment not only for arbuda but for all other associated diseases as well. Ayurvedic principle emphasizes on the complete removal of vitiated *dosas* in order to maintain their equilibrium and thus preserving patients immunity (*rogibala*). Although detoxification is pre-therapy but it's not fit for all patients. Patients with severe illness cannot tolerate therapeutic emesis or purgation. Thus, these procedures contradict with general treatment.

Scientists tried to elucidate the role of detoxification therapies on cancer patients as pretherapy to conventional line of treatment. Several studies showed that these detoxification procedures increased body weight, improved serum immunoglobulins, increased hemoglobin levels, and normalized liver functions. Thus, in combinational therapy where Ayurveda and chemotherapy are given together, detoxification was found helpful in minimizing the adverse effects of chemotherapeutic agents. The studies recommended the following procedures for the treatment of cancer:

1. Oleation therapy (*snehana*): Medicated ghee prepared with *triphal* (*Terminalia chebula, Terminalia bellerica, Emblica officinalis*) in patients with breast cancer.
2. Therapeutic purgation (*virechana*): in malignant hepatobiliary system disorder.
3. Medicated enema (*basti karma*): in malignant genitor-urinary system [15].

Table 1: Some common Ayurvedic preparations for the treatment of tumours

Name of the Formulation	Main Constituents	Indication	Dose	Ref.
Lokanatha rasa (brihat)	Mercury, sulphur, mica, aloe, iron oxide ground with *Solanum*	Mentioned in liver and spleen disorders	125–250mg twice/ day	[16]

	nigrum			
Rudra rasa (arbudahara rasa)	Mercury and sulphur ground with the decoctions of betel leaf, boerhavia, cow's urine, *Piper longum*, and amaranthus	Mentioned in all types of cancer	125–250 mg twice/day	[17]
Manashila	Arsenic disulphide	For external application on tumors	Quantity sufficient	[18]
Tamra basma	Colloidal copper	Used in all types of intra-abdominal swellings (*gulma*)	15–125 mg[a]	[19]
Abhraka basma	Mica	Mentioned in all types of debilitating diseases	125–250 mg[a]	[20]
Suvarna basma	Gold dust	Used to improve immunity, strength, and body weight	2.5–6.0 mg[a]	[21]

*As directed by the physician.

Above-mentioned formulations contain metals, which may pose threat to human health. These types of formulations were developed Buddhist practitioners around 7-8 century, but their safety and efficacy are yet to be validated by modern science. but modern science still formidable evidence to accept them as safe.

Classical treatment procedures in Ayurveda

Classical Ayurvedic formulations contain multiple herbs that have huge potential for cancer cure. Such formulations can work on several biochemical pathways that may stimulate several organ systems at the same time. Using multiple herbs in a single formulation has the benefit of nourishing the whole body by supporting various organ systems. Apart from polyherbal combinations fomentations, cauterisation, scraping, bloodletting, medicated enemata and other surgical procedures were also applied as classical[22]. Whereas habitual intake of *Basella rubra* or application of alkali preparation of *Musa paradisiaca*, *Conch shell ash*, *Elaeocarpus tuberculatus*, *Sulphur*, *Potassium carbonate*, *Embelia ribes* and *ginger* for the eliminations of *arbuda* were considered as traditional method.

Table 2 contains classical treatment protocols for various tumors in Ayurveda and Table 3 is the compilation for various herbal combinations mentioned in Ayurvedic literatures. The main purpose of these tables is to promote the use of these conventional approaches as well as natural medicines for successful cancer treatment by physicians and researchers.

Table 2 Traditional treatment methods for different types tumours in Ayurveda.

Types of Tumors	Tumor Subtypes	Classical Treatment Procedures
Arbuda	*Medoja arbuda*	*Curcuma domestica*, *Triticum sativum*, *Symplocos racemosa*, etc. powder externally applied by mixing them with honey. Oil from *Pongamia glabra* were used for internal administration [23]
	Kaphaja arbuda	A drug which removes doshas from both ends (vomiting and purgation) was used after surgical removal of tumour. A decoction of the leaves *Clitoria ternatea*, *Jasminum grandiflorum and Nerium odorum* was then used for purification. The oil cooked with *Premna herbacea*, *Embelia ribes*, *Cissampelos pareira* has been used for postoperative treatment.

	Vataja arbuda	Mixture of *Benincasa cerifera*, *Cucumis memordica*, *Cocos nucifera*, and *Eranda beeja*, *Ricinus communis* along with butter or milk were applied [23]
	Pittaja arbuda	Tumours were first treated with Ficus *glomerata*, *Tectona grandis*, and *Elephantopus scaber* leaves repeatedly. After that with a honey mixed fine paste of *Aglaja roxburghiana*, *Caesalpinia sappa*, *Symplocos racemosa*, *Terminalia arjuna*, *Xanthium strumarium* was applied [22]
Granthi	*Vatika granthi*	*Helloborus niger*, *Tinospora cordifolia*, *Clerodendron serratum*, *Aegle marmelos*, *Hoya viridiflora*, *Elephantopus scaber*, *Soymida febrifuga* and *Gynandropis pentaphylla*were used in local application[22]
	Kapaja granthi	*Capparis spinosa*, *Capparis sepiaria*, *Agati grandiflora*, *Lagenaria vulgaris*, *Premna herbacea*, *Pongamia glabra*, *Musa sapientum* and *Randia dumetorum* paste used locally [22]
	Paittika granthi	Powder of *Terminalia chebula* was used orally either with grape or sugarcane juice. The paste of *Glycyrrhiza glabra*, *Eugenia jambolana*, *Terminalia arjuna* or *Calamus rotang* were used externally [22]

Table 3 List of herbs widely used in Ayurveda for treating cancer

Name of the herb	Method and use
Curcuma domestica	~~The~~ *Curcuma domestica* powder in combination with *Symplocos racemosa*, *Soymida febrifuga*, is mixed with honey for external application [14]
Moringa oleifera	In arbuda tumours, the paste of *Moringa oleifera* seeds, *Solanum xanthocarpum*, *Sinapis dichotoma*, *Holarrhena antidysenterica* and *Nerium odorum* roots prepared with buttermilk is used[14]
Ficus bengalensis	Mixture of *Ficus bengalensis* and *Saussurea lappa* is applied to pacify tumour development on bone[14]
Flacourtia romantchi	For *kaphaja* tumours,the paste of *Flacourtia romantchi*, *Cassia fistula*, *Capparis sepiaria*, is recommended [5]
Basella rubra	A preparation of the plant and leaves with sour buttermilk with salt is indicated for *arbuda* [5]
Oxoxylum indicum	The herb *Oxoxylum indicum* is prescribed in treatment of *granthi* [5]
Amorphopallus campanulatus	For tumour removal, the mature tuber is first burnt and then mixed with butter and jaggery and then applied on the affected area [5]
Prosopis cineraria	For disintegrating cysts, The paste of *Prosopis cineraria* seeds, *Raphanus sativa*, *Moringa oleifera*, barley and mustard with sour buttermilk was applied locally [11]
Barleria prionitis	Oil prepared from *Barleria prionitis* whole plant is recommended for external application during acute stages of cyst in blood vessels [11]
Pterospermum acerifolium	For local application, *Pterospermum acerifolium* flowers were mixed with sugar.
Pandanus odoratissimum	For external use, paste of *Pandanus odoratissimum* with sugar was used[14]
Madhuca indica	A paste prepared from the barks of *Madhuca indica*, *Syzygium cumini*, *arjuna Terminalia arjuna* and *Salix caprea* is recommneded for local application[14]
Baliospermum montanum	A paste consisting of *Baliospermum montanum*, *Plumbago zeylanica*, *Euphorbia neriifolia*, *Calotropis procera*, jaggery, *Semecarpus anacardium* is used over the tumours[14]
Vitis vinifera	Traditionally a mixture of *Terminalia chebula*, grape juice and *sugar cane juice* has been used [3]. However, Resveratrol, a derivative from grape juice has shown to have cancer chemo preventive activity [24]

Oncoprotective role of Ayurvedic herbs

Numerous herbs are mentioned in Ayurveda to treat various types of tumors or cancers. Some herbs have protective role while other herbs contain phytochemicals that are used in the treatment of cancers since ancient times. Vitro studies show tremendous potential of Ayurvedic herbs in the protection as well as treatment of cancer. Many herbs described below have scientifically proven onco-protective role.

Withania somnifera

Roots of *W. somnifera* contains Withaferin A. Withaferin A was found effective be in Ehrlich ascitis carcinoma when given at a dose of 30 mg/kg along with radiation therapy [25]. Withaferin A and the alcoholic extract of dried roots of *W. somnifera* showed synergistic antitumor and radio-sensitizing effects in experimental tumors *in vivo*. These effects didn't show any detectable systemic toxicity although the mechanism of action is still not understood well. Results from the studies indicate that *W. somnifera* could be a promising natural source of a potent and pretty safe radio-sensitizer and chemotherapeutic agent.

It is also proved that *W. somnifera*, in addition to having a tumor-inhibitory effect, also acts as a radio sensitizer [26]. *W. somnifera* extract also inhibited 20-methylcholanthrene-induced sarcoma development in mice at a dose of 20 mg/day [27]. *W. somnifera* extract was also found to be effective in reducing two-stage skin carcinogenesis induced by DMBA and croton oil [28].

When 75% methanolic extract of *W. somnifera* was administered in normal Balb/c mice, it increased the total white blood cell (WBC) count significantly. It also reduces the leucopenia induced by a sub-lethal dose of gamma radiation. *W. somnifera* treatment was found to significantly increase the bone marrow cellularity in mice. Irradiated mice normalized the ratio of normochromatic erythrocytes and polychromatic erythrocytes when treated with *W. somnifera*. However, the major activity of *W. somnifera* is more pronounced in the stimulation of stem cell proliferation [29].

Other than its role on anticancer therapy, *W. somnifera* extract was also found effective as a chemopreventive agent. *W. somnifera* protected against 20-methylcholanthrene-induced fibrosarcoma tumors in Swiss albino mice. Thorough Liver biochemical parameters analysis revealed a significant changeover of reduced glutathione, lipid peroxides, glutathione-S-transferase, catalase, and superoxide dismutase in extract-treated mice compared with 20-methylcholanthrene-injected mice. The authors suggested that *Withania somnifera* extract's mechanism of chemopreventive activity might be due to its benign growths, cysts, and malignant tumors antioxidant and detoxifying properties [30].

Aloe vera Linn.

Aloe vera is a very common herb frequently used in cosmetic industries; especially in hair and skin care products. One of the active components of *Aloe vera* is Di (2-ethylhexyl) phthalate (DEHP). This compound has been shown to have antileukemic and antimutagenic effects *in vitro* in

Salmonella typhimurium TA98 and TA 100 strains [30]. Aloes also potentiated the antitumor effect of 5-fluorouracil and cyclophosphamide as components of combination chemotherapy [31]. Another compound Aloe-emodin (hydroxyanthraquinone), widely found in *Aloe vera* leaves has been shown to have a specific *in vitro* and *in vivo* anti-neuroectodermal tumor activity [32].

Other than being used as cosmetic product *Aloe vera* reported to have several important therapeutic properties, including anticancerous effects. The effect of this drug on a pleural tumor in rats (Yoshida AH-130 ascite hematoma cells) was studied and its therapeutic use in cancer was proved [33].

Some researcher showed Aloe vera's antigenotoxic and chemopreventive effect. In one such study, the antigenotoxic and chemopreventive effect of *Aloe barbadensis* Miller (polysaccharide fraction) on benzo[a]pyrene (B[a]P)-DNA adducts was investigated *in vitro* and *in vivo*. Aloe showed a time-course and dose-dependent inhibition of [3H]B[a]P- DNA adduct formation in primary rat hepatocytes ($1x10^6$ cells/ml) treated with [3H]B[a]P (4 nmol/ml) [34].

Coleus forskohlii

Preventing metastasis is a major challenge in cancer treatment. Forskolin, a diterpene isolated from C. forskohlii, has been found to strongly inhibit the melanoma cell-induced human platelet aggregation and tumor colonization. The study suggests that forskolin could prove to play a major part in the hospital for the prevention of cancer metastasis [35].

Andrographis paniculata Nees

The methanol extract of the Andrographis paniculata Nees aerial component showed powerful cell differentiation-inducing activity on mouse myeloid leukemia (M1) cells [36].

Santalum album

Santalum album is a very famous ayurvedic herb, widely used in cosmetic industry especially in skin care. The essential oil, emulsion, or paste of S. album has been used in India as an Ayurvedic medicinal agent for the treatment of inflammatory and eruptive skin diseases. Sandal wood-oil treatment showed chemo preventive effect in DMBA-initiated and TPA-promoted skin papillomas tumor model and TPA-induced ornithine decarboxylase (ODC) activity in CD-1 mice. Sandalwood-oil treatment significantly decreased papilloma incidence by 67%, multiplicity by 96%, and TPA-induced ODC activity by 70%. The study indicates that the oil could be an efficient chemo-preventive agent against skin cancers [37].

Picrorrhiza kurroa

In 20- methylcholanthrene (20 MC)-induced tumor model, P. kurroa extract has been shown to have antitumor and anticarcinogenic activity after oral administration. Transplantable tumours were also inhibited by the P.kurroa extract [38].

Sesame Oil

Sesame oil is extensively used as topical application in Ayurveda for skin health. In one of the study, it was found that sesame and safflower

oils, both of which contain significant amounts of triglyceride-like linoleate, selectively inhibited the growth of malignant melanoma over normal melanocytes; coconut, olive and mineral oils, which contain little to no triglyceride-like linoleate, did not. Further studies revealed that only linoleic acid was selectively inhibitory, whereas palmitic and oleic acid were not. These fatty acids were tested in the range of 3 to 100 mg/ml. The study indicates that some linoleic acid-rich vegetable oils, such as sesame oil, recommended for topical use by Ayurveda, can in fact contain selective antineoplastic properties [39].

Terminalia arjuna

In vitro studies show that methanol extract of T. arjuna inhibited the growth of human normal fibroblasts (WI-38), although it didn't have any effect on normal cells. In transformed cell A cyclin-dependent kinase inhibitor, p21WAF1, was induced by T. arjuna. It is speculated that T. arjuna has natural components that can inhibit of transformed cell by p53-dependent and independent pathways [40–41].

Andrographis paniculata

The known diterpenes (andrographiside and neoandrographolide) isolated from this plant and it's crude have showed their potential against tumourigenesis by their anti-lipoperoxidative action and by enhanced carcinogen detoxification action [42–43].

Annona atemoya/muricata

Annona atemoya has many potential anti-tumour compounds. One such compound is Bullatacin, an acetogenin isolated from the fruit of *Annona atemoya*, induces apoptosis, preceded by chromatin margination and tumour cells condensation [44]. Several other annonaceous acetogenins, e.g. muricins A–G, muricatetrocin A and B, longifolicin, corossolin, and corossolone have showed their potential in bringing in selective vitro cytotoxicities to tumour cells [45].

Phyllanthus niruri/amarus

P. amarus aqueous extract increases the life span of the tumour bearing rats and normalizes gamma-glutamyl transpeptidase activity [46]. It also plays a key role in disruption of HBsAg mRNA transcription and post-transcription which could be beneficial against viral carcinogenesis [47].

Piper longum

One of the active alkaloid of piper longus is piperine. Piperine has antioxidant property. Because of this antioxidant potency, piperine has been used as an ingredient of ayurvedic anticancer formulations in both in vitro and in vivo conditions [48].

Podophyllum hexandrum linn. (Podophyllin)

It's active ingredient podophyllin is a powerful anticancer drug (e.g. sarcomas, adenocarcinoma and melanoma). Podophyllin and its active principle, podophyllotoxin exerts their cytotoxic effect by mitotic inhibition, nuclear fragmentation, impaired spindle formation properties. In some cases and they are also found to be karyoplastic. The mode of action of this cytotoxic effect has been termed as necrosis and it works directly a on tumour tissues [49].

Now a days, chemically synthesized podophyllotoxins are extensively used in varies

cancer therapies. VP-16 (etoposide), a derivative of podophyllotoxin is being used against hepatic cancers for more than a decade after getting promising data against *in vitro* and *in vivo* cancer cells [50]. It's efficacy has been proven its in in phase II studies together with epirubicin [51]. After using this combinatorial therapy at least 3% of the patients had recovered completely whereas 36% responded with partial or least toxic effects. P-glycoprotein, a pump for the drug efflux, tends to be less effective in reducing the concentration of VP-16 in cancer cell lines and it works more successfully in these cells [52].

Tinospora cordifolia

The active ingredient from *T. cordifolia* enhances host immune system by increasing immunoglobulin and blood leukocyte levels. It also stimulates of stem cell proliferation to increase host immune response. It has the capacity to reduce solid tumour by 58.8%, which is equivalent to cyclophosphamide, a well-known chemotherapeutic agent [53–54]. These immune stimulating properties can be used in preventing tumour-mediated immune suppression and could therefore be a drug choice for different cancers

Semecarpus anacardium

In ancient Ayurveda texts, *Semecarpus anacardium* nuts has been mentioned in numerous occasions because of their anticancer properties [55]. In recent years many review mention the phytochemical and pharmacological properties of *S. anacardium* [56]. The chloroform extract of *S. anacardium* nut is known to have anti-tumour activity with extension of life span against leukaemia, melanoma and glioma [57–58]. The milk extract of *S. anacardium* regresses hepatocarcinoma by stimulating host immune system [59] and normalises tumour markers including alpha-fetoprotein[60]. During cancer progression, this preparation stabilizes the lysozomes, and normalizes glycoprotein and mineral content in the body [61–62]. It is also found to control abnormal lipid peroxidation [63] by the maintaining antioxidant defence status [64]. Its action as a bifunctional inducer in the microsomes of both phase I and II biotransformation enzymes prevents tumour initiation by preventing carcinogen activation [65]. Histologically,when hepatocarcinoma animals were treated with *S. anacardium* extract, the nodules were completely regressed and further necrosis of cell was prevented [66].

Anacartin forte, another active ingredient from *S. anacardium* has been used as an anticancer drug for several decades, as it improves health by alleviating or disappearing of critical symptoms. It gives clinical advantage with an extension of survival time in diverse cancers including oesophageal, persistent myeloid leukaemia, urinary bladder and liver cancer [67]. Another Ayurvedic preparation containing *S. anacardium*, *Amura rohitaka, Glycyrrhiza glabra* and copper powder had been reported to inhibit breast tumour development in mice by significantly extending the lifespan. Clinical trial of this drug was also found to be efficient and promising [68].

Ayurvedic herbs, commonly used and scientifically proven for their effectiveness against

cancer, are presented in Table 4. Smit et al. [69] have also complied ayurvedic and herbal drugs reported to have anticancer activity. Some of these herbs have shown to increase the therapeutic effectiveness and/or reduce the toxicity of anticancer drugs used together in chemotherapy. Also, a handful of them known to have radio-sensitizing effect too (see Table 4). Table 5 compiles the pharmacological details of ayurvedic herbs like their therapeutic dosage, side effects, and comments about safety and herb-drug interactions. Beside these, specific herbal parts with anti-tumour activities are also mentioned in Table 6 and 7.

Table 4: Scientific evidence of Ayurvedic herbs having anticancer property

Name of the Herb	Indications	Ref.
Albizzia lebbeck	Sarcoma of bone and tissue 180 (mice)	70
Abrus precatorius	Yoshida sarcoma (rats) Fibrosarcoma (mice) Ascites tumour cells.	71
Allium sativum	Sarcoma (rat)	72
Aloe vera	Yoshida AH-130 ascites hepatoma (pleural tumour) human neuroectodermal tumours	73–74
Alstonia scholaries	HSI human sarcoma benzo(a)pyrene induced forestomach carcinoma	70, 75
Amura rohitaka	Leukaemia	76–77
Anacardium occidentale	In liver cancer commonly known as hepatoma 129	70
Asparagus racemosa	Human epidermoid carcinoma	70
Bacopa monniera	Walker carcinosarcoma 256	78
Berberis aristata	Human epidermal carcinoma of the nasopharynx *N*-nitrosodiethylamine induced carcinogenesis	78–79
Boswellia serrata	Human epidermal carcinoma of the nasopharynx Leukaemia and brain tumours.	70, 80
Calotropis gigantea	Human epidermal carcinoma of the nasopharynx.	70, 78
Curcuma longa	Fibrosarcoma Preclinical and clinical trials review	81–82
Datura metel	Human epidermal carcinoma of the nasopharynx	70
Erythrina suberosa	SARCOMA 180	70
Euphorbia hirta	Freund virus leukaemia	70
Gynandropis pentaphylla	Hepatoma 129	70
Heliotropium indicum	P-388 lymphocytic leukaemia	83
Hygrophila spinosa	Dalton's lymphoma Ehrlich ascites carcinoma and Sarcoma-180	84–85
Ixora undulata	P-388 lymphocytic leukaemia	86
Juniperus indica	Human epidermoid carcinoma of the nasopharynx	86
Luffa cylindrica	Schwartz leukaemia	87
Melia azedarach	Walker carcinosarcoma 256	87
Moringa oleifera	Human epidermoid lymphocytic leukaemia Skin papillomagenesis	86–88
Nerium indicum	Erlish ascites carcinoma	83
Nigella sativa	Lewis lung carcinoma Colon cancer	70–89
Ocimum sanctum	Skin and liver tumours	90
Paederia foetida	Human epidermoid carcinoma of the nasopharynx	70
Picrorrhiza kurroa	Hepatic cancers	70
Plumbago zeylanica	Hepatoma	91
Rubia cordifolia	P-388, L-1210, B-16 melanoma, colon 388, Lewis lung carcinoma, mammary carcinoma	92
Taxus buccata	Cytotoxic against various tumours	93
Vinca rosea	P-1534, carcinoma of the breast, cervix, kidney, lung and ovary	94
Withania somnifera	Various tumours	70

Table 5: Synergistic effect of ayurvedic herbs on cancer chemotherapy/radiation

Name of the herb	Synergistic effect studies of ayurvedic herbs on Chemotherapy/radiation
Allium sativum	S-allylmercaptocysteine (SAMC) a water soluble derivate of garlic, inhibited proliferation and cell cycle progression in two human colon cancer cell lines, SW-480 and HT-29 and these effects are similar to sulindac sulfide (SS), a very well-known colon cancer chemo preventive agent. When SS is Co-administered with SAMC an enhanced the growth inhibitory and apoptotic effects of SS was observed, suggesting the effictiveness of SAMC alone or in combination with SS or other chemopreventive agents [95]
Aloe vera	In a randomized double-blind clinical trial, contrasting mild soap and aloe vera gel against occurrence of radiation therapy induced skin reactions, it took a median period of five weeks to display any skin changes in aloe / soap treatment compared to three weeks in soap treatment only. When added to the soap, aloe vera also exerts its protective effect during long time radiation exposure [96]. In some other clinical trial where patients with advanced solid tumours, for whom no other standard effective therapy was available, combination of pineal indole melatonin (MLT) plus Aloe vera extracts showed some potential therapeutic benefits, at least in terms of stabilization of disease and survival when compared to MLT treatment alone [97]
Alstonia scholaris	The effect of radiation was increased by pre-treatment with *Alstonia scholaris* extracts which is manifested by enhancement of cell killing in HeLa and KB cells, followed by HL60, MCF7, and HePG2 cells. In vivo studies showed that Ehrlich ascites carcinoma bearing mice with the pre-treatment of extract extended the life span of animal when compared with untreated irradiated group [98]. When Ehrlich ascites carcinoma was treated with a combination of both *Alstonia scholaris* extract and cyclophosphamide, it showed most effectiveness and caused the highest tumour regression and enhanced the mean and average survival time when compared with cyclophosphamide alone [99]
Curcuma longa	Curcuma had a radiation-sensitive effect in HeLa, K-562 and IM-9 cell lines when radiation and curcuma were added together as synergy therapy[100]. Curcumin, one of the active component from *Curcuma longa* also reported to increase the anticancer potential of Cisplatin and reduces its nephrotoxicity in fibrosarcoma bearing rats [81]
Heliotropium indicum	In a Phase I study of solid tumor patients with previous chemotherapy / radiation treatment, Indicine N-oxide, a Heliotropium alkaloid indicum, showed some improvement against skin melanoma and ovarian carcinoma [101]
Moringa oleifera	When mice received pre-treatment with the *M. oleifera* leaf extract, it showed marked radiation protection to the bone marrow chromosomes and this could be used to circumvent the side effects of radiation therapy [102]
Nigella sativa	The main constituent of *Nigella sativa* oil is thymoquinone (TQ). When mice bearing Ehrlich ascites carcinoma is treated with thymoquinone, it significantly enhanced the efficacy of ifosfamide by improving its antitumor effect and also reduced its nephrotoxicity. Moreover, mice treated with a ifosfamide and TQ, it showed less body weight loss and mortality rate compared to IFO alone.[103]
Ocimum sanctum	Two water-soluble flavonoids isolated from the leaves of *Ocimum sanctum* namely Orientin and Vicenin have shown protective effect against the clastogenic effect of radiation, radiation lethality and chromosomal aberrations in vivo to human lymphocytes. Such radio protective activity may be associated with their antioxidant activity and may have therapeutic use in cancer.[104]
Taxus buccata	In a Phase II study, when a combination of taxol (active constituent of *Taxus buccata*), ifosfamide, and carboplatin was applied to patients with advanced stage IIIB-IV non-small-cell lung cancer, it proved its effictiveness and safety along with ease to deliver[105]. Interestingly combination of Herceptin with Taxol markedly enhances the overall response rate, increases the time to progression and the overall survival in breast cancer patients. These effects are more pronounced in patients characterized with HER/2^{+++} over expression [106]. Besides taxol also exhibits a weak radio sensitising effect on breast and cervical carcinoma cells on the basis of an optimal Taxol/radiation scheduling [107]
Withania somnifera	When *W. somnifera* was administered for 4 days before paclitaxel treatment and continued for 12 days, it significantly reversed the neutropenia of paclitaxel in mice. In addition, it can be used as an adjuvant for the prevention of bone marrow depression associated with anticancer drugs during cancer chemotherapy. Withaferin A, the active component isolated from the *W. somnifera* extract showed significant antitumour and radiosensitising effects in experimental tumours in vivo, without any remarkable systemic toxicity [25–30].

Table 6 List of Ayurvedic herbs and herbal extracts with antitumor activity

Botanical Name	Used parts	Action mentioned in Ayurvedic classic	Action proven by scientific experiments	Ref.
Semicarpus anacardium	Fruit	excises unhealthy tissues, rejuvenator	Has potential antitumor activity towards experimental mammary carcinoma in animals	108
Withania somnifera	Root	Reduces swellings, rejuvenator	Alcoholic root extract in doses of 400 mg / kg and above causes complete regression of the skin in two stages.	28
Crocus sativa	Stamens	reduces swellings, rejuvenator	Has antitumor activity against solid tumors of sarcoma-180 and Ehrlich ascites carcinoma (EAC) in mice	109
Ocimum sanctum,	Leaf, seed, root	detoxifies, reduces swellings, purifies vitiated blood	Reduces 20-methylcholanthrene-induced tumor incidence and tumor volume	110
Calotropis, procera,	Root, latex, flower	pacifies vitiated *kapha*, reduces swellings, purifies *vitiated* blood, detoxifier	Displays the strongest cytotoxic effect with ID_{50} values of 1.4 micro gm/ml	69
Plumbago rosea	Root bark	*Lekhana* (excises unhealthy tissue), *shothahara* (reduces swellings), *rasayana* (rejuvenator)	Used together with radiation to facilitate the tumor-killing effect.	111
Cassia fistula	Fruit pulp, root bark	*Kaphashodhaka* (pacifies vitiated *kapha*), *shothahara* (reduces swellings)	Increases life span by decreasing the tumor volume and viable tumor cell count in the EAC tumor hosts;improves the hematological factors after methanolic extract treatment, like hemoglobin content, red blood cell count and bone marrow cell count of the tumor- bearing mice	112
Aloe vera	Leaf	Kaphahara (pacifies vitiated *kapha*), *shothahara* (reduces swellings), *vrana ropana* (heals wounds), *raktashodhaka* (purifies vitiated blood)	Detoxifies reactive metabolites including chemical carcinogens and drugs	113
Bambusa arundinacea	Root, leaf, Shoot	*Kaphashamaka* (pacifies vitiated *kapha*), *lekhana* (excises unhealthy tissue), *vishaghna* (detoxifier)	Antitumor activity against benzopyrene and 4-nitroquinolince-1-oxide-induced tumours is reported. Maximum effect obtained with 1% bamboo leaf extracts (0.71 mg/ml). These indicates direct action of bamboo leaf extracts on tumor cells.	114
Ferula narthex	Latex	*Kaphahara* (normalizes vitiated *kapha*)	Asafoetida is an effective antioxidant that can provide defence against free radical induced diseases such as cancer.	115
Trigonella foenum-Graecum	Seed	*Shothahara* (reduces swellings)	Has an anti-inflammatory and antineoplastic effect	116

***Emblica officinalis* Gaertn**	Fruit	*Shothahara* (reduces swellings)	Antioxidant, antitumor, chemopreventive, prostate cancer, immunomodulator, anticlastogenic radiation protection.	[117]

Table 7 Pharmacological particulars of reported Ayurvedic anticancer herbs [118–120].

Name of the herb	Recommended therapeutic dose	Safety/duration/ toxic dose	Side effects/ contraindications	Interactions with other herbs/drugs
Allium sativum	2–5 g per day, solid extract: 0.3–1 g, oil: 0.03–0.12 ml t.i.d.	Likely safe	Can cause stomach upset when used in excess. May increase the chance of hemorrhagic complaint.	Chances of interaction with aspirin
Aloe vera	Extract: 10–20 ml, powder: 0.05–0.2 g	Safe for short term therapy	Intake over the long term will exacerbate ulcers, haemorrhoids	Reported to interact with cardiac glycosides and diuretics
Andrographis paniculata	Powder: 1.5–6 g, juice of leaves and stem: 1–4ml t.i.d., andrographolide: 4–6 mg	Safe	Nausea, anorexia, emesis, Urticaria	Interaction with anticoagulant and antihypertensive drugs/herbs
Berberis aristata	Powder: 1–3 g	Chances of being toxic at higher dosage	Possibly cause lethargy, nose bleeds, nausea, vomiting, diarrhoea	Possible interference with Vitamin B assimilation
Calotropis cylindric	0.5–1 g	Likely unsafe	Vomiting, diarrhoea, bradycadia	Can interact with cardioactive herbs and horsetail
Curcuma longa	1.5–3.0 g	Safe, non-toxic	Contraindicated in gastric ulcers	No interactions reported
Datura stramonium	0.05–0.1 g	Likely unsafe	Vomiting, hypertension, loss of consciousness. May lead to coma	Possibility of interaction with anti-cholinergic drugs
Euphorbia hirta	Powder: 0.12–0.3g, liquid extract: 0.1–0.3 ml	No information about safety. Tolerable dose: up to 1 g/i.p. in mice	Nausea, vomiting, dermatitis with skin contact	No interactions reported
Ficus religiosa	Powdered bark: 1–3g, liquid extract: 60–120 ml	Likely safe at given dosage	Large amounts can cause catharsis/allergies	None reported
Hygrophila spinosa	Seed powder: 2–8g, liquid extract: 40–50ml	Insufficient information available	Sufficient data not available	Sufficient data not available
Juniperus communis	2–10g per day	Limit to maximum of 6 weeks Likely safe for short term	Long term may cause kidney damage	May interact with anti-diuretic drugs
Nigella sativa	1–3 g	Safe	No adverse effects known	No interactions cited.
Ocimum sanctum	1–3 g, leaf infusion: 4–12ml	Likely safe	Long term uses likely to cause constipation at higher dosage	Not reported
Phyllanthus niruri	Powder 3-6g	Safe	None known	None reported
Piper longum	0.5–1 g	Likely safe	Possibility to have contraceptive activity therefore advised refrain from using	Active ingredient Piperine may interact with enzymatic drug biotransformation

			during pregnancy and lactation	
Plumbago zeylanica	1–2 g	Plumbagin LD_{50} 10mg/kg in mice, whole plant: 0.5g/kg/i.p.	None reported	None known
Raphanus sativus	15–23 g, liquid extract 50–100 ml	Likely safe	Excessive dose may cause irritation of GI mucus membrane	No interaction reported
Semecarpus anacardium	Oil: 1–2 drops, fruit: 0.5–1.5 g	Likely unsafe	Anacardic acid may cause allergy to some people	Not enough data
Tinospora cordifolia	Powder: 1–3 g, liquid extract: 56–112 ml	Safe	Nausea	Over dose might inhibit Vitamin B assimilation
Vinca rosea	Dosage depends on severity of the disease	Likely unsafe	GI upset, hepatotoxicity, nausea, vomiting, may also cause hypoglycemia	No interactions reported so far.
Vitis vinifera	0.15–0.3 g	Safe	None reported	None known
Withania somnifera	2–6 g	Likely unsafe	Nausea, dermatitis, abdominal pain, diarrhoea	Possibility to enhance the action of barbiturates and benzodiazepines

CONCLUSION

A lot of medicinal plants used as ayurvedic drugs showed clinical efficacy in the treatment of tumour or cancer having least side effects comparing to the synthetic drugs. So, it is worthy to use and promote ayurvedic drugs for the treatment of cancer. Beside these, more extensive studies are indispensable to explore the in-depth molecular knowledge concerning the mode of action of each ayurvedic drugs in line of cancer or tumour treatment.

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