REVIEW ARTICLE

Role of ayurveda in tumorigenesis: A brief review

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From ancient times, many herbal compounds have been screened worldwide to validate their use as anticancer drugs. But an integrated approach is required along with complete knowledge about the disease. Hence, an attempt has been made in this review to discuss about the role of Ayurveda in cancer therapy. Also, discussion about the pathology and therapeutic management of various cancers described in Ayurveda has been made in this review. Review of literature on anticancer drugs of plant origin revealed identification of newer several Ayurvedic drugs that can be used for the treatment of one of the most dreaded diseases, i.e. cancer.

Key words: Ayurveda, cancer, integrated, therapy

INTRODUCTION

Cancer is a hyperproliferative disorder that involves transformation, dysregulation of apoptosis, proliferation, invasion, angiogenesis and metastasis. Extensive research during the last 30 years has revealed much about the biology of cancer.[1] Cancer, also known medically as a malignant neoplasm, is a large group of different diseases, all involving unregulated cell growth. In cancer, the cells divide and grow uncontrollably, forming malignant tumours, and invade the nearby parts of the body.[2] Cancer is one of the most dreaded diseases which is increasing its influence in the 21st century. Multidisciplinary scientific investigations are making the best efforts to combat this disease, but the sure-shot, perfect cure is yet to be brought into world medicine. Recently, a greater emphasis has been given towards the researches on complementary and alternative medicine that deals with cancer management. Several studies have been conducted on herbs under a multitude of ethnobotanical grounds. For example, Hartwell[3-11] has collected data on about 3000 plants, those of which possess anticancer properties and subsequently have been used as potent anticancer drugs.[12] The term "Ayurveda," which is derived from Sanskrit (the ancient language of India) – "ayus" (life) and "ved" (knowledge) – is often translated as science of life and is a 5000-year-old system of Indian medicine. It emphasises on the prevention of disease, rejuvenation of body systems and extension of lifespan. It has been successful from very early times in using these natural drugs and preventing or suppressing various tumours using various lines of treatment.

This article reviews a summary of treatment strategy in Ayurveda for various cancers.

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PATHOGENESIS OF CANCER

Before the review of pathogenesis of cancer, cell cycle has to be reviewed as the cancer mainly affects the normal cell cycle of the body.

Cell Cycle

G1 and G2 (gap 1 and gap 2) are characterised by protein and RNA synthesis, but no DNA synthesis. S (synthesis) is the period of DNA synthesis. M (mitosis) is the period when the nucleus and then the rest of the cell divide [Figure 1].

Genetic abnormalities found in cancer typically affect two general classes of genes:

1. Cancer-promoting oncogenes are often activated in cancer cells, giving those cells new properties, such as hyperactive growth and division, protection against programmed cell death, loss of respect for normal tissue boundaries, and the ability to become established in diverse tissue environments.
2. Tumour suppressor genes are often inactivated in cancer cells, resulting in the loss of normal functions in those cells, such as accurate DNA replication, control over the cell cycle, orientation and adhesion within tissues, and interaction with protective cells of the immune system.[13] The cancer pathogenesis has been shown in Figures 2 and 3.

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Cancer according to Ayurveda

Charaka and Sushruta Samhita (700 BC) both described the equivalent of cancer as *granthi* (benign or minor neoplasm) and *arbuda* (malignant or major neoplasm).[14-16] Both can be inflammatory or non-inflammatory, based on the *doshas* involved.[17] The term *dosha* describes the three principles that govern the psychophysiological response and pathological changes in the body. The balanced coordination of these three systems (*vata*, *pitta* and *kapha*) in body, mind and consciousness is the Ayurvedic definition of health.[18] The fundamental theory of Ayurvedic treatment is based on restoration of the balance between these three major bodily systems. Tridoshic tumours are usually malignant because all three major body humours lose mutual coordination, resulting in a morbid condition.[19,20]

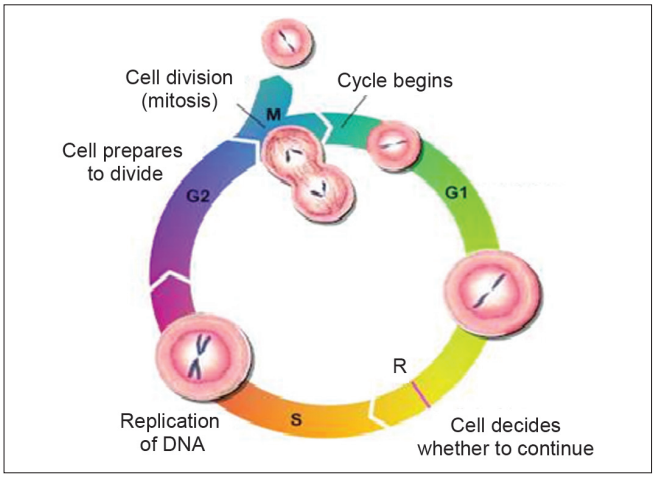

Figure 1: Cell cycle

Pathogenesis of Cancer according to Ayurveda

Pathogenesis in Ayurveda is explained on the basis of *tridoshas*. *Agni* or *pitta*, which is present in each and every cell, is responsible for digestion and metabolism in human body.

The decrease in *agni* is inversely proportional to the related tissue, and therefore in *arbuda*, the decreased state of *dhatwagni* (deranged metabolism) will result in excessive tissue growth. *Vata* can be correlated with the anabolic phase of growth, and *kapha* with the catabolic phase. Cancer originates due to a metabolic crisis, i.e. aggravation of *vata* forces and suppression of *kapha* forces, both interacting

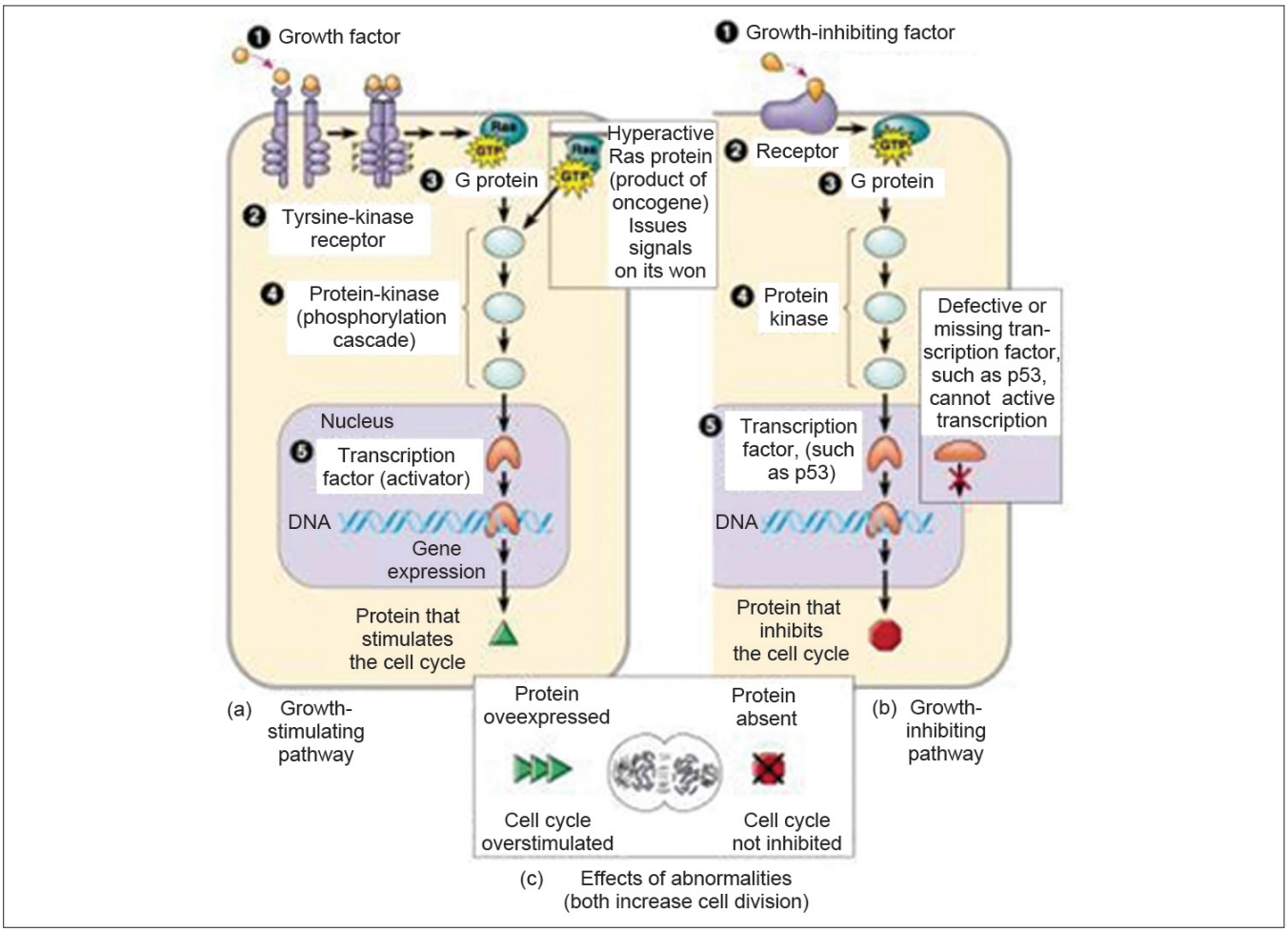

Figure 2: Pathogenesis of cancer

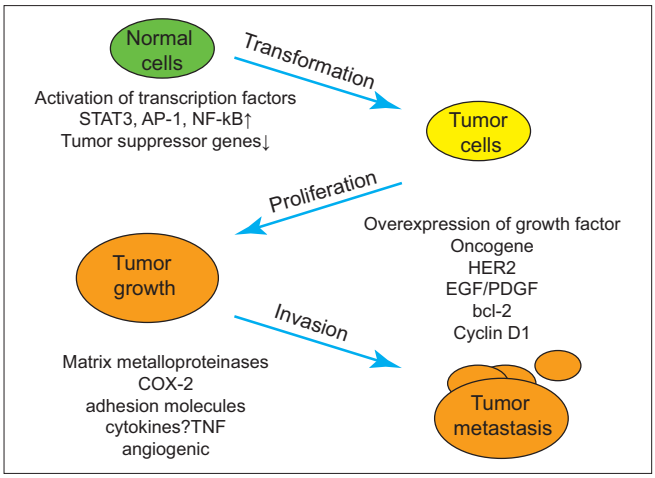

Figure 3: Tumorigenesis

with one another resulting in proliferation. However, the abnormal cancerous growth at a specific organ (*Ekadesavriddhi*) is managed by compensation from other parts of the body (*Anyasthaniyakshaya*), e.g. body weight loss (cachexia).[21] Sushruta has proposed six stages in the pathogenesis of all diseases, but his concept suits more to the pathology of the tumour than the pathogenesis itself.

1. *Sanchaya*: Early stages of localised neoplastic changes
2. *Prakopa*: Transformation of primary growths into metastatic tumours
3. *Prasara*: Metastasis
4. *Sthana samsraya*: Complete metastasis and secondary growth
5. *Vyakti*: Clinical signs and symptoms are expressed
6. *Bheda*: The stage where differentiation of growth occurs on the basis of histopathology[21]

CLASSIFICATION OF NEOPLASMS ACCORDING TO AYURVEDA

Ayurvedic classification of neoplasms depends upon various clinical symptoms in relation to *tridoshas*.

- Group I: Diseases that can be named as clear malignancies, including *arbuda* and *granthi*, such as *mamsarbuda* (sarcomas) and *raktarbuda* (leukaemia), *mukharbuda* (oral cancer), and *asadhya vrana* (incurable or malignant ulcers).
- Group II: Diseases that can be considered as cancer or probable malignancies, such as ulcers and growths. Examples of these are *mamsaja oshtharoga* (growth of lips), *asadhya galganda* (incurable thyroid tumour), *tridosaja gulmas*, *asadhya udara roga* (abdominal tumours like carcinomas of the stomach and liver or lymphomas).
- Group III: Diseases with the possibility of malignancy, such as *visarpa* (erysipelas), *asadhya kamala* (incurable jaundice), *asadhya pradara* (intractable leucorrhoea) and *tridosaja nadi vrana* (intractable sinusitis).[19,22]

FACTORS RESPONSIBLE FOR THE VITIATION OF THE *TRIDOSHAS*

The factors responsible for the vitiation of *doshas* are:[21]

a. *Vata* aggravating factors: Excessive intake of bitter, pungent, astringent, dry foods and stressful conditions.
b. *Pitta* aggravating factors: Excessive intake of sour, salty, fried foods and excessive anger.
c. *Kapha* aggravating factors: Excessive intake of sweet, oily food and sedentary nature.
d. *Rakta* aggravating factors: Excessive intake of acid or alkali containing foods. Fried and roasted foods, alcoholic beverages, sour fruits are some examples. Excessive anger or severe emotional upset, sunbathing or working under scorching sun or near fire and hot conditions, etc. are some other causes.[23]
e. *Mamsa* aggravating factors: Excessive use of exudative foods like meat, fish, yoghurt, milk and cream. Behaviours leading to exudation like sleeping during the day and overeating are some of the causes for pathogens invading the fatty tissues.[23]
f. *Medo* aggravating factors: Excessive intake of oily foods, sweets, alcohol and lazy attitude.[23,24]

GENERAL MECHANISM OF ACTION OF SOME AYURVEDIC ANTICANCER DRUGS

Sukh Dev (1992),[25] in collaboration with a group in USA, studied Triphala using I-125 cholecystokinin (CCK) as ligand and mouse pancreatic membrane as receptor. They showed affinity of three Ayurvedic herbal extracts – *Terminalia chebula* (96% ligand displacement), *Terminalia bellerica* (91%) and *Phyllanthus emblica* (76%), showing that "Triphala" constituents act on CCK receptors. Charaka states: "A single drug may have many applications owing to its diverse actions just as a man is able to perform various actions". Many popular Ayurvedic drugs such as Ashwagandha, Bramhi, Guduchi, Katuka, Shatavari, etc. have multivarious properties ascribed to them. Obviously, their molecular targets are shared by many cell systems and cell membrane components such as phospholipase A2, phospholipase C, adenylyl cyclase and cAMP, adenosine receptors, eicosanoids, ion channels, and neuroreceptors such as dopamine, serotonin, norepinephrine (NE), gamma-aminobutyric acid (GABA), etc. Stress-activated protein kinase (SAPK2) is an enzyme highly activated by bacterial lipopolysaccharides and cytokines. Many Ayurvedic Rasayan drugs act by blocking this enzyme and prevent downstream activation of nuclear factor (NF)-kB. Interestingly, NF-kB pathway activation is common to both inflammation and cancer.

Dahanukar and Thatte[26] made pioneering contribution by showing immunomodulatory action of Amlaki,

Ashwagandha, Guduchi, Haritaki, Pipalli and Shatavari, all of which are now shown to suppress NF-kB activation and regulate chronic dysregulated NF-kB pathway. Curcumin and ginger have been studied extensively to elucidate their action at the molecular level.

SOME AYURVEDIC SOURCES OF ANTI CANCER DRUGS

Some of the herbs used in Ayurveda have been shown in and Table 1 and Figure 4.

1. *Andrographis paniculata*: The extract and isolated diterpenes (andrographiside and neoandrographolide) from this plant are proved to be beneficial against tumorigenesis by their anti-lipoperoxidative action and by enhanced carcinogen detoxification action.[29-32]
2. Guggulsterone (*Commiphora mukul*): Guggulsterone [4,17(20)-pregnadiene-3,16-dione] is a plant sterol derived from the gum resin (guggulu) of the tree *Commiphora mukul*. The resin has been used in Ayurvedic medicine for centuries to treat a variety of ailments, including obesity, bone fractures, arthritis, inflammation, cardiovascular disease and lipid disorders.[33,34] The antiarthritic and anti-inflammatory activities of gum guggul were demonstrated as early as 1960 by Gujral *et al*.[35] Sharma *et al*. showed guggul's activity in experimental arthritis induced by a mycobacterial adjuvant.[36] The effectiveness of guggul for treating osteoarthritis of the knee also has been demonstrated.[37] Recent studies have shown that guggulsterone is an antagonist for the bile acid receptor, farnesoid X receptor.[38,39] Other studies have shown that guggulsterone enhances transcription of the bile salt export pump,[40] thereby regulating cholesterol homeostasis.

   Guggulsterone suppresses DNA binding of NF-kB induced by tumour necrosis factor (TNF), phorbol ester, okadaic acid, cigarette smoke condensate, hydrogen peroxide, and interleukin (IL)-1. Guggulsterone also suppresses the constitutive NF-kB activation expressed in most tumour cells. In addition, guggulsterone decreases the expression of gene products involved in antiapoptosis [inhibitor-of-apoptosis protein-1 (IAP1), X chromosome-linked IAP, Bfl-1/A1, bcl-2, cFLIP and survivin], proliferative genes (cyclin D1, c-myc) and metastatic genes [matrix metalloproteinase (MMP)-9, cyclooxygenase (COX)-2 and vascular endothelial growth factor (VEGF)]. This is correlated with the enhanced apoptosis induced by TNF and chemotherapeutic agents.[41]
3. *Phyllanthus niruri/amarus*: An aqueous extract of *Phyllanthus amarus* increases the life span of the tumour-bearing rats and normalises glutamyl transpeptidase activity.[42] It plays a major role in disruption of HBsAg mRNA transcription and post-transcription, which could be beneficial against viral carcinogenesis.[43]
4. Curcumin (*Curcuma longa*): Curcumin (diferuloylmethane) is an active component of turmeric (*Curcuma longa*), which has been used as a spice and as an Ayurvedic

Table 1: Commonly used *Ayurvedic* herbs in cancer

Name of the herb	Method and use
Vitis vinifera	The mixture of *Terminalia chebula*, grape juice and sugarcane juice has been used.[5] Resveratrol, a natural product derivative from grape juice, has been proved to possess cancer chemopreventive activity[27]
Baliospermum montanum	The paste comprising *Baliospermum montanum*, *Plumbago zeylanica*, *Euphorbia neriifolia, Calotropis procera*, jaggery, *Semecarpus anacardium* applied over the tumours[24]
Madhuca indica	This paste is prepared from the barks of *Madhuca indica*, *Syzygium cumini*, Arjuna *Terminalia arjuna* and *Salix caprea* and is prescribed for local application[24]
Pandanus odoratissimum	A paste of *Pandanus odoratissimum* with sugar was applied externally[24]
Pterospermum acerifolium	The flowers of *Pterospermum acerifolium* mixed with sugar to be applied locally
Raphanus sativus	Local application of *Raphanus sativus* powder paste with the radish ash was considered effective against *kaphaja arbuda*
Barleria prionitis	The *Barleria prionitis* oil prepared with whole plant is indicated for external application during acute stages of cyst in blood vessels[28]
Prosopis cineraria	This paste made up of *Prosopis cineraria* seeds, *Raphanus sativa*, *Moringa oleifera*, barley and mustard with sour buttermilk is applied locally for disintegrating cysts[28]
Amorphopallus campanulatus	The mature tuber is first burnt and then mixed with butter and jaggery and applied for tumour destruction[28]
Oxoxylum indicum	The drug *Oxoxylum indicum* prescribed in the treatment of *granthi*[28]
Basella rubra	The plant and leaves are ground with sour buttermilk with salt for preparing a poultice and indicated for *arbuda*[28]
Flacourtia romantchi	The paste of *Flacourtia romantchi*, *Cassia fistula*, *Capparis sepiaria* is recommended for *kaphaja* tumours[28]
Moringa oleifera	The paste of *Moringa oleifera* seeds, *Solanum xanthocarpum*, *Sinapis dichotoma*, *Holarrhena antidysenterica* and *Nerium odorum* roots prepared with buttermilk is used for *arbuda* tumours
Ficus bengalensis	Application of mixture of *Ficus bengalensis* and *Saussurea lappa* pacifies tumour growth on bone[25]
Curcuma domestica	The *Curcuma domestica* powder in combination with *Symplocos racemosa* and *Soymida febrifuga* is mixed with honey and this is used as an external remedy[25]

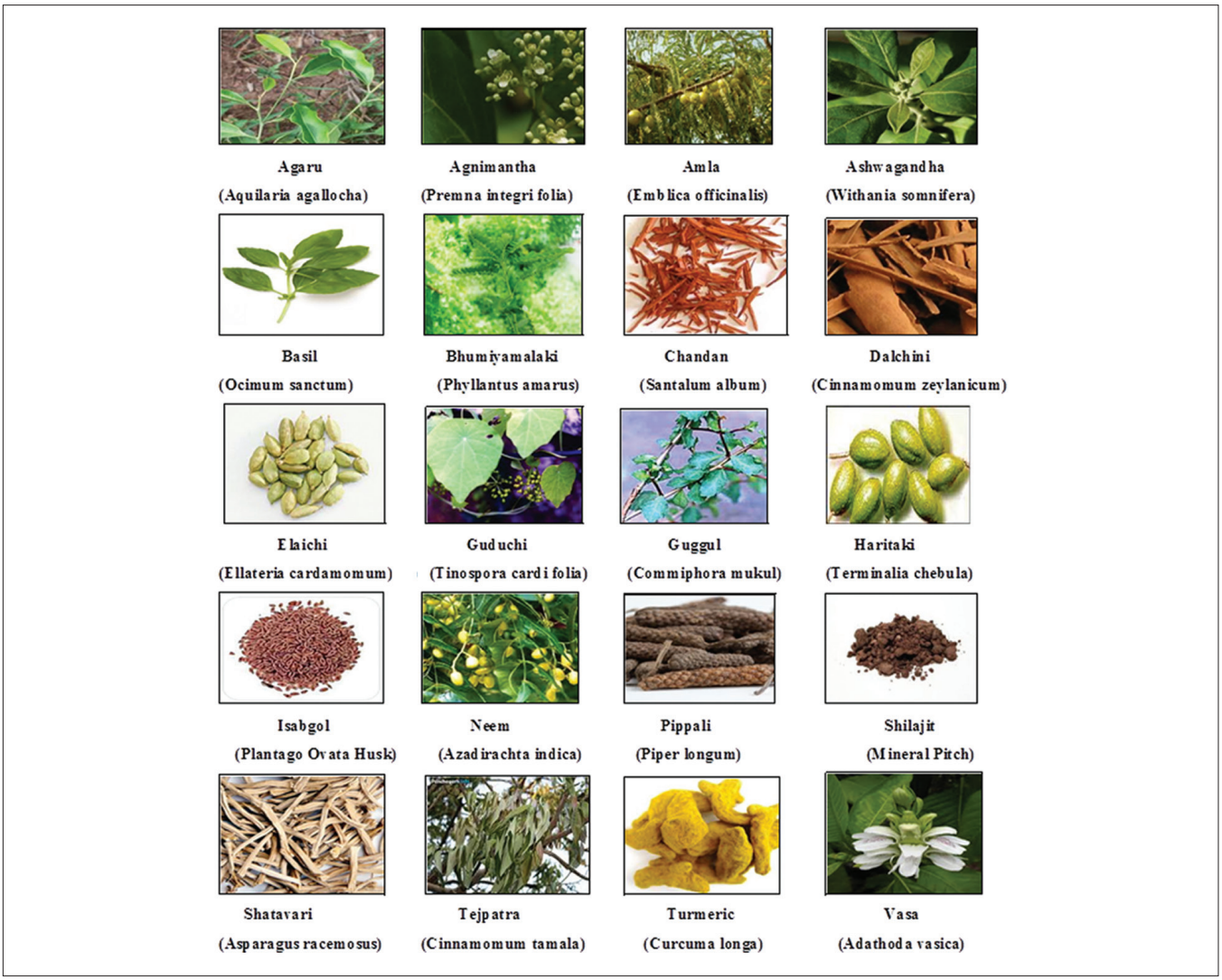

Figure 4: Herbal drugs of Ayurveda

medicine for centuries in the Indian subcontinent. Curcumin has been shown to suppress carcinogenesis of the skin, liver, lung, colon, stomach and breast. It has also been shown to inhibit the proliferation of a wide variety of tumour cells in culture and to promote apoptosis through Bid cleavage, cytochrome-*c* release, caspase-9 activation and then caspase-3 activation.[44-65] Curcumin mediates this wide variety of therapeutic effects by regulating the transcription factors NF-kB and activator protein, suppressing IkBa kinase and c-Jun N-terminal kinase, and inhibiting the expression of COX-2, cyclin D1, adhesion molecules, MMPs, inducible nitric oxide synthase (iNOS), human epidermal growth factor receptor 2 (HER2), epidermal growth factor receptor (EGFR), bcl-2, bcl-XL and TNF.

5. *Piper longum*: Piperine, an active alkaloid extracted from this plant, has been used as an ingredient of Ayurvedic anticancer formulations because of its antioxidative potency in both *in vitro* and *in vivo* conditions.[66]
6. Withanolide (*Withania sominifera*): The medicinal plant *Withania sominifera* is widely known for its anti-inflammatory, cardioactive and CNS effects. In Ayurveda, withanolides, which are extracted from *W. sominifera*, are employed in the treatment of arthritis and menstrual disorders and are known to be potent inhibitors of angiogenesis, inflammation, tumour development, metastasis and oxidative stress, and a promoter of cardioprotection. Many pharmacological studies have investigated the properties of *W. sominifera* in an attempt to authenticate its use as a multipurpose medical agent. Experimental studies have shown that *W. sominifera* possesses anti-inflammatory, anti-tumour, cardioprotective and antioxidant properties. Withaferin A, one of the compounds in the withanolide family, is a potent inhibitor of angiogenesis. It also appears to exert a positive influence on the endocrine, urogenital and central nervous systems. In recent years, herbal formulations containing substantial amounts of *W. sominifera* root extract have been evaluated in small clinical trials and are shown to have efficacy in the

treatment of osteoarthritis. Extracts are also known to significantly inhibit tumour growth *in vivo*. Withanolide also enhanced the apoptosis induced by TNF and chemotherapeutic agents and suppressed invasion. These results indicate that withanolide inhibits activation of NF-kB and NF-kB–regulated gene expression.[1]

7. *Podophyllum hexandrum* Linn. (Podophyllin): It is a powerful anticancer drug against various cancers, e.g. sarcomas, adenocarcinoma and melanoma. Podophyllin and its active principle, podophyllotoxin, are known for their cytotoxic effect by virtue of their properties of mitotic inhibition, nuclear fragmentation, impaired spindle formation, and they are also found to be karyoplastic. The mechanism of action has been suggested as necrosis and is a direct consequence of its cytotoxic effect on tumour tissues. These derivatives have been analysed in cancer chemotherapeutic studies, and the methods of preparation of these compounds are patented.[11] Nowadays, chemically modified podophyllotoxins are widely used in cancer therapeutics. VP-16 (etoposide), a podophyllotoxin derivative, has been tested against *in vitro* and *in vivo* cancer cells and been used against hepatic cancers for more than a decade.[67] It has proved its efficacy in combination with epirubicin in phase II studies.[68,69] By this combination therapy, at least 3% of the patients had complete cure and 36% had partial response. P-glycoprotein, a drug efflux pump, seems to be less effective in reducing VP-16 concentration in cancer cell lines, and hence this drug proves to be more efficient in these cells.[70] It is also safe even above therapeutic dosage without much toxic effects.[71]
8. Boswellic acid (*Boswellia serrata*): Boswellic acid (BA) is an active component of *Boswellia serrata* (also known as Salai guggul). The gum resin of this plant is used in Ayurvedic medicine to treat rheumatic diseases, respiratory diseases and liver disorders.[72-74] Extensive research within the last 30 years has identified the active component of this resin as BA (a pentacyclic triterpenic acid) and its derivatives [acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid (AKBA)].[75,76] The traditional therapeutic usefulness of BA is a result of its anti-inflammatory activity, possibly mediated through the inhibition of 5-lipoxygenase (5-LOX)[76-78] and leukocyte elastase.[79,80]
9. *Tinospora cordifolia*: The active principles from *Tinospora cordifolia* enhance host immune system by increasing immunoglobulin and blood leucocyte levels and by the stimulation of stem cell proliferation. It has the ability to reduce solid tumour volume by 58.8%, which is comparable to cyclophosphamide, a known chemotherapeutic agent.[81-83] These immune stimulating properties can be used in the prevention of tumour-mediated immune suppression, and hence could be a drug choice for various cancers.
10. *Semecarpus anacardium*: In Ayurveda classics, numerous references are available on the anticancer properties of *Semecarpus anacardium* nuts.[84] An extensive review describes the phytochemical and pharmacological properties of *S. anacardium*.[85] The chloroform extract of *S. anacardium* nut possesses anti-tumour action with increased life span against leukaemia, melanoma and glioma.[86,87] The milk extract of *S. anacardium* produces regression of hepatocarcinoma by stimulating host immune system[88] and normalising tumour markers including alpha-fetoprotein levels.[89,90] This preparation stabilises the lysozomes, and normalises glycoprotein and mineral content in the body during cancer progression.[91,92] It also corrects hypoglycaemia[93] and controls abnormal lipid peroxidation[94] by the maintenance of antioxidant defense status.[95] In the microsomes, it acts as a bifunctional inducer of both phase I and II biotransformation enzymes and prevents tumour initiation by preventing carcinogen activation.[96,97] Histologically, on treatment with the *S. anacardium* extract to hepatocarcinoma animals, the liver sections showed almost a normal architecture. The nodules became completely regressed and further cell necrosis was prevented.[98] Anacartin forte, another preparation from *S. anacardium*, has been used for several decades as an anticancer drug since it gives health improvement with alleviation or disappearance of troublesome symptoms. It provides clinical benefit with an extension of survival time in various cancers including oesophageal, chronic myeloid leukaemia, urinary bladder and liver cancer.[99] Another Ayurvedic drug containing *S. anacardium*, *Amura rohitaka*, *Glycyrrhiza glabra* and copper powder was reported to inhibit breast tumour development in mice by significantly extending the survival period. This drug was also found to be efficient in clinical trials.[22]

CONCLUSION

This review presents evidence that agents derived from plants used in Ayurvedic medicine can be used not only to prevent cancer, but also to treat cancer. Because of their pharmacological safety, these agents can be used alone or as adjuncts to current chemotherapeutic agents to enhance therapeutic effects and minimise chemotherapy-induced toxicity. Because cancer is primarily a disease of older age, finding less toxic therapies is a major priority. Tumour cells use multiple cell survival pathways to prevail, and Ayurvedic agents that can suppress these multiple pathways have great potential in the treatment of cancer. The evidence indicates that most of the plant-based agents used in Ayurvedic medicine do indeed suppress multiple pathways. More research is needed in order for these agents to reach their full therapeutic potential.

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