CHAPTER 26

Therapeutic Effects of Ayurvedic Medicines for the Treatment of Different Cancers

MUHAMMAD FAISAL HAYAT[1], MUHAMMAD UMAR IJAZ[1*]

[1]Department of Zoology, Wildlife and Fisheries, University of Agriculture, Faisalabad, Pakistan.
Correspondence: umar.ijaz@uaf.edu.pk

SUMMARY

The Ayurvedic system is an integrated system of medicines that has been present all over the world for thousands of years. It has gained popularity in recent years owing to its plant-based natural remedies against various sorts of diseases. Cancer is a leading cause of death worldwide therefore, research for effective treatments became a root cause for the emergence of Ayurvedic medicines as potential therapies. Studies have shown that several Ayurvedic medicinal plants possess anti-cancer properties and can be effective in preventing the growth and spread of cancer cells. Some of the commonly used Ayurvedic herbs for cancer treatment include Ashwagandha, Mangosteen, Turmeric, and Amla. These herbs have been found to contain bioactive compounds that have anticancer effects by reducing inflammation, inducing apoptosis, and inhibiting angiogenesis. Ayurvedic medicines have been used not only in humans but also in animals for cancer treatment. In veterinary medicine, Ayurvedic treatments have shown promising results in treating various cancers, including mammary gland tumors, skin tumors, and oral tumors in dogs and cats. Ayurvedic medicine, however, is not a one-size-fits-all solution for cancer treatment. It is crucial to consult an experienced Ayurvedic practitioner to determine the right treatment plan based on the individual's health condition and the stage of cancer. Moreover, it is essential to understand that Ayurvedic medicine should not be used as a replacement for conventional cancer treatments but as a complementary therapy. However, with further research, Ayurvedic treatments can potentially play a vital role in the prevention and management of cancer all over the world.

INTRODUCTION

Ayurveda is a Sanskrit word meaning “Science of Life” which provides various sorts of therapies and treatments for different diseases as well as enhances the health status of people (Dahanukar & Thatte 1989; Dahanukar & Thatte 1996). The Ayurvedic system is an integrated and comprehensive system of herbs that has been in practice for many years Fig 1. Ayurvedic system is one of the most traditional systems of medicine in India which is based on 3 major components (i) Pitta (ii) Vayu and (iii) Kapha. There are numerous ayurvedic medicines along with their therapeutic actions such as Amalaki which is used to diminish the impacts of aging as well as provide a balanced diet (DravyaGuna, 2009). Pitta describes all the aspects related to intelligence as well as transformation, for instance, an individual has certain types of ulcers, infections, and inflammation. Pitta indicates abnormalities of the digestive system, anxiety, and arthritis while Kapha overlooks the physical aspects of the body such as congestive disorders and overweight.

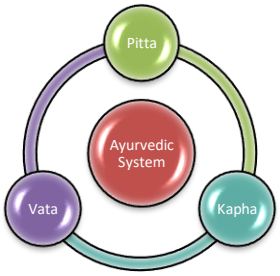

Fig 1. Integrative system of Ayurveda with its core components.

HISTORICAL BACKGROUND OF AYURVEDA

The Atharva-Veda is the first legitimate work to examine the essence of existence, health, illness, etiology as well as

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treatment approaches. It is the fourth Veda to be authored during Indian civilization. The healing hymns of Ayurveda are predominantly found in this section of the Atharva-Veda, where more than 100 hymns are cited as treatments for ailments such as high temperature, cardiac failure, chronic wounds, leprosy, parasitic infection, eyes as well as ear infections, intoxication, arthritis, and seizures. The enormous diversity of healing techniques employed by this traditional medicinal system includes charms, plants and animal fluids, natural forces (sun and water), as well as human inventions (Svoboda, 1992). Ayurveda's origins can be dated to the time between the pre-Vedic periods. According to Ayurveda vatarana (the descent of Ayurveda), Daksha Prajapati and Ashwins were the first who received Lord Brahma (Hindu God of Creation) meaning knowledge of life," which was later handed on to Indra. Thereafter, several rishis (sages) received this information, and these students of Ayurveda created various treatises (books/principles) based on their assessments. Later on, Bhardwaj and Dhanvantari both learned the information from Indra and established schools for surgery and medicine respectively (Dahanukar & Thatte 1989).

In the early nineteenth century, studies were executed to extricate and change active components from the natural herbs as a consequence, chemical and analytical techniques became available which led to the formation of emerging pharmaceutical products from natural herbs and their ingredients (Tab. 1.1). During this period, the use of herbal remedies began to decrease (Ehrlich, 2011). Despite the potent pharmacological efficacy, synthetic medications are proven to be comparatively more costly and have a wide range of undesirable effects. As a result, many practitioners turned back to herbal medicines because these medications proved harmless and are derived naturally (Oreagba et al., 2011). There are three major categories of ayurvedic medicines based on the source material: herbal, minerals, and animals. Among these, herbal formulations have recently grown substantially and gained worldwide attention. This prospect has gained immense success in the past several years and the market revenue of herbal medicines significantly expanded in the United States and European nations (Kamboj, 2000). According to the World Health Organization (WHO), 80 percent of the global population still primarily depends on traditional medications for their therapeutic potential (Mathew & Babu 2011).

DIFFERENT AYURVEDIC MEDICINES AND THEIR ROLE IN CANCER TREATMENT

Cancer is considered the primary cause of disease-related deaths in the world and these numbers are increasing day by day. Epidemiological information provided by GLOBOCAN in 2018 reported 9.6 million mortalities due to cancer along with 18.1 million newly reported patients (GLOBOCAN, 2018). It is estimated that these rates of mortality and new cases per annum will exceed 17 and 26 million respectively by 2030 (Thun et al., 2010).

Tab 1. Various Ayurvedic plants and their anti-cancerous activities

Ayurvedic Plant	Activity	Reference
Albizzia lebbeck	Suppress gallbladder tumor	(Haque et al., 2000)
Withania somnifera	Anti-proliferative action against MCF-7 cell line of breast carcinoma	(Jayaprakasam et al., 2003)
Cassia fistula	Inhibit tumor growth in ascites carcinoma	(Gupta et al., 2000)
Azadirachta indica	Enhance anti-proliferative action against different cancer cell lines in human	(Roy et al., 2007)
Saraca indica	Suppress skin cancer growth	(Cibin et al., 2010)
Xantium strumarium	Anti-proliferative action against lung cancer cell line NCL-417	(Ramírez-Erosa et al., 2007)

Amalaki

Amalaki (*Phyllanthus emblica Linn*) is considered as most potent antioxidant herb in the Ayurvedic system with low molecular weight. Amalaki has strong scavenging action against reactive oxygen species owing to the high composition of vitamin C. It is reported to show anti-cancerous potential against different types of cancers such as human breast cancer, prostate, colon, hepatic, lung, and gastric cancer. Fruits of *P. emblica* extract was studied to investigate its impacts on activator protein-1 as well as papillomavirus of humans that are core stimulators of tumorigenesis in cervical cancer cell lines. *P. emblica* is documented to inhibit the DNA binding ability of constitutively activator protein-1 in HPV18-positive and HPV16-positive cell lines of cervical cancer. The development of cervical cancer cells was inhibited as a result of AP-1 inhibition brought about by *P. emblica* suppression of viral transcription. *P. emblica* growth-inhibitory effect mostly showed up by triggering apoptotic cell death (Mahata et al., 2013). Furthermore, Amlaki is documented to enhance the potential of natural killer cells in mice with lymphoma ascites tumors. Administration of Amlaki increased the lifespan of tumor-bearing mice (Suresh et al., 1994).

Ashwagandha

Ashwagandha is generally known as the Indian winter cherry (Singh et al., 2011) and belongs to the Solanaceae family (Palliyaguru et al., 2016). Ashwagandha is reported to have been used as a tonic before 3000 BC in Indian continents (Tab. 1.2). Root extract of Ashwagandha is documented to show anti-cancerous effects in different experimental models (Shohat et al., 1967). Numerous investigations demonstrated the anti-

angiogenic as well as anti-metastatic properties of different extracts of Ashwagandha. It has been reported that Withaferin-A (a derivative of Ashwagandha) shows inhibitory activities in mesothelioma (Yang et al., 2012). Withaferin-A suppressed the growth of tumors in malignant pleural mesothelioma in Withaferin-A administrated animals, which suggested its targeting as well as inhibitory potential against the propagation of tumors. In another investigation, Withaferin targeted vascular endothelial growth factor (VEGF) and demonstrated its anti-VEGF potential indicating its anti-angiogenic potential (Saha et al., 2013). Withaferin-A has also been shown to prevent the propagation of breast cancer by altering metabolic pathways. It is proved that Withaferin-A minimizes the size of tumor in metastatic lung cancer (Hahm et al., 2013; Wadhwa et al., 2013; Gao et al., 2014).

Withaferin-A is reported to degrade 56-kDa protein in the cells of human umbilical vein endothelial cells and thus designated as vimentin which is an important component of intermediate filament that regulates the processes of angiogenesis, tumor propagation, a healing process of the wound as well as metastasis (Eckes et al., 2000; Yokota et al., 2006; Beijnum et al., 2006). It was reported that Withaferin-A binds to vimentin directly and causes the protein to degrade. In addition, similar effects were observed on other filament proteins, including KIFs (keratin heteropolymer IFs), PFs (peripherin filaments), NIFs (neurofilament triplet protein) as well as VIFs (vimentin inhibitory filaments). According to the research conducted by Grin et al. (2012), cells treated with Wi-A developed more actin stress fibers which disrupted their microtubules and microfilaments eventually led to the death of cells.

Tab 2. Composition of Ashwagandha

Constituents	Percentage	References
Linoleic acid	44 %	(Arora et al., 2011)
Oleic acid	28.40 %	
Linolenic acid	8.78 %	
Saturated fatty acids	7 %	
Unsaponifiable matter	3.81 %	
Palmitic acid	2.99 %	
Sterol	2.70 %	
Stearic acid	2.15 %	
Myristic acid	0.95 %	
Fat	0.1 %	(Ghosal, 1996)
Fiber	3.4 %	
Carbohydrates	14.1 %	
proteins	0.5 %	
Vitamin C	600mg/ 100g	(Jeena et al., 2001)
Calcium	0.05 %	

Activation of nuclear factor-kappa B (NF-kB) regulates the different processes such as metastasis, carcinogenesis, proliferation of cells, and inflammation in the body. The activation of NF-kB is suppressed by an inhibitor (IkB) which establishes a complex with NF-kB and keeps it in the cytoplasm. Phosphorylation of IkB-by-IkB kinase (IKK) breaks down its complex with NF-kB and thus promotes its activation (Karin and Delhase 2000). IkB kinase consists of two subunits IKKα and IKKβ as well as a regulatory subunit known as NF-kappa-B essential modulator (NEMO). Withaolide (a derivative of Ashwagandha) is reported to attack the binding pockets of NEMO such as Glu89, Glu99, Ala 100, Leu 93, Phe92, and Phe 97. These interactions disrupt the ratio of NEMO: IKKβ (Grover et al., 2010b). Additionally, the combined administration of dichloro-diphenyl-trichloroethane (DDT) and Withaferin-A mitigates the inhibitory effects of Withaferin-A against the activation of NF-kB via the TNF pathway (Kaileh et al., 2007).

After lung cancer in terms of the frequency of cases reported in males, prostate cancer accounted for 3.8 percent of all cancer-related fatalities in 2018. (Bray et al., 2018). Active components of *Withania somnifera* have been shown to have a variety of anticancer effects. For instance, Withaferin-A combines with other anti-androgens inducing prostate cancer cells to undergo prostate apoptotic response-4 (Par-4) dependent apoptosis that led to the recovery of PC-3 xenografts in mice (Srinivasan et al., 2007). Moreover, Withaferin-A decreases cell survival rate in a dose-dependent manner and accumulates Wee1 in the G2/M phase of the cell cycle (Roy et al., 2013).

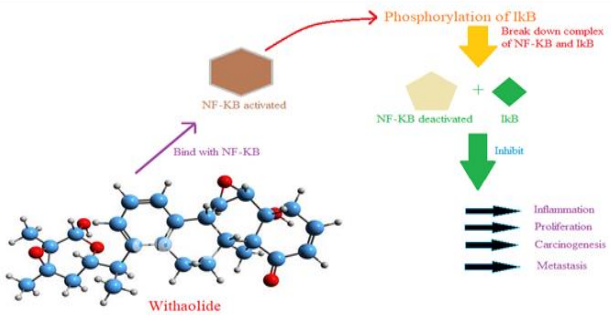

Fig 2. Mechanisms of deactivation of NF-KB by Withaolide in cancerous cells.

Mangosteen

A sharp escalation in the prevalence of skin carcinoma such as non-melanoma as well as melanoma is a significant public health concern (Trakatelli et al., 2007; Doan, 2008). The aging population and higher levels of ultraviolet radiation penetration to the surface of the earth as a consequence of ozone layer depletion are major contributors that escalate the incidence of skin cancer (Miller & Weinstock 1994; Johnson et al., 1998). Thus, it's crucial to build novel and powerful chemo-preventive drugs that can diminish or perhaps stop the spread of skin cancer. Around 50% of the anti-cancer medications now being tested in numerous experiments are influenced by natural

materials, particularly land plants (Cragg & Newman 2000; Nuijen et al., 2000; Gordaliza, 2007). South-east Asia is the native place of mangosteen (*Garcinia mangostana Linn.*). Southeast Asians and South Americans have employed its pericarp for millennia as a form of traditional medicine to cure a wide range of illnesses, including diarrhea, wounds, and skin problems (Pedraza-Chaverri et al., 2008; Obolskiy et al., 2009). In neuroblastoma cells (NG108-15) which exposed to oxidative stress owing to the production of H_2O_2, ethanolic extract of mangosteen pericarp (50%) is reported to demonstrate neuroprotective as well as antioxidative potential (Weecharangsan et al., 2006).

Another ethanolic extract of the mangosteen pericarp decreased the production of prostaglandin E_2 (Nakatani et al., 2002), histamine, as well as HIV-1 protease (Chen et al., 1996). Methanolic extract of mangosteen pericarp demonstrated apoptotic, antioxidative, and anti-proliferative properties against (SKBR3 cell line) breast cancer (Moongkarndi et al., 2004a). The pericarp of mangosteen contains both xanthones and anthocyanins while xanthones constitute the majority of the bioactive substances (Nguyen et al., 2005). Furthermore, several investigations show the marvelous action of xanthones against cytotoxicity due to several kinds of cancers such as colorectal, leukemia, hepatoma, and lung cancer (Akao et al., 2008; Pedraza-Chaverri et al., 2008; Obolskiy et al., 2009). The aforementioned ethanolic extract is reported to elevate the activity of antioxidant enzymes as well as demonstrate anti-cancerous activity against aforementioned skin cancers (Wang et al., 2012).

Frankincense

The cultivation of frankincense was initiated in ancient times during monsoon season in various regions of the world such as India, Somalia, the Peninsula, and Ethiopia while it was traded via European and China routes. Frankincense, also referred to as olibanum is extortionate due to its scarcity and thus considered as a symbol of a plethora of wealth. Olibanum is considered an antique and high demand as well as a precious resource in the European region. The word frankincense is derived from two French words “franc” and “encens” which means pure and noble respectively. The oleogum resin is extensively used in catholic churches for different purposes such as for funeral ceremonies or for the treatment of different illness which includes constipation, flatulence, disease of the nervous system, gastric diseases as well as respiratory disorders (Martinez et al., 1989).

Pills formulated from frankincense are extensively used in nasopharyngeal, bronchial, and pancreatic carcinomas (de-Visser et al., 2006). Since 2006, frankincense has been used as an approved anti-inflammatory drug in Europe and it is placed as the 7th essential supplement of European Pharmacopoeia. Pharmacological, phytochemical, and clinical studies have been conducted on frankincense since the 1980s to explore its potential therapeutic role against different diseases (Ammon, 2016). Many medicines have eventually become resistant over time thus the need for new anti-resistant medicine is the main reason for the aforementioned studies (El-Seedi et al., 2019; Efferth et al., 2007). Different extracts of frankincense demonstrated various sorts of activities, for instance, Boswellia extract which is also known as Indian frankincense is used as a strong therapeutic agent against cancer cell lines during in-vitro and in-vivo investigations. Furthermore, the Boswellia extract of frankincense is reported to demonstrate anti-cancerous action against various sorts of carcinoma such as breast, prostate, hepatic, lung, and cervix as well as suppressing the growth of tumors thus designated as a strong tumor growth inhibitor during in-vivo investigations. Boswellia extract of frankincense and its derivatives reduced excessive production of reactive oxygen species thus ultimately diminishing the oxidative stress (Park et al., 2002; Estrada et al., 2010) as well as elevating the level of stress markers such as heat shock proteins and GRP78 (Hussain et al., 2009; Ni et al., 2012). Boswellia extract of frankincense is documented to cause demethylation of DNA as well as induce the expression of histone core protein (Thorsteinsdottir et al., 2011). It is also involved in the inhibition of transduction signaling such as activated protein kinase, protein kinase b expression, STAT3, dephosphorylation of ERK1/2, focal adhesion kinase as well as ribosomal protein S6 kinase (Mazzio et al., 2017; Conti et al., 2018; Park et al., 2011).

Cancer treatment by nano-ayurvedic medicines

Nano-herbal medications can generally refer to nano-formulations that contain herbs. A plethora of research has recently been produced that examines the structural as well as functional characteristics of several kinds of nanoparticles. These nanoparticles can be molded and stabilized in a variety of ways for use in the biomedical field. The ability of metallic nanoparticles to treat cancer has recently been documented in several investigations. Silver and gold nanoparticles among metal nanoparticles have long been recognized for their pharmacological activity. For their potential use in cancer treatment and diagnostics (or "theranostic") applications, gold nanoparticles have received substantial research (Gharatape and Salehi, 2017). Remarkably, these aggregation-resistant nanomaterials exhibit significant anticancer activities and intriguing modes of action even when stabilized with ordinary substances like citrate or tryptone.

For instance, gold nanoparticles stabilized with tryptone showed marvelous potential to arrest cell division in cancerous cells of the pancreas at both the G1 and S phases (Mahaddalkar

et al., 2017). In this scenario, coupling these particles with a medication that induces cell cycle arrest in the G2/M phase may help to eradicate cancer cells with stochastic cell cycle dynamics. The capacity of these nanoparticles to annihilate triple-negative breast cancer (TNBC) cells preferentially is another remarkable finding. Triple-negative breast cancer cells differ from normal cells in that they contain many centrosomes. These extra organelles (centrosomes) also known as supernumerary centrosomes which aid cancer cells in remodeling their cytoskeleton, promoting migration and metastasis (Nirmala and Lopus, 2019). The development of "targeted therapy" is being facilitated by modern medicine's recognition of the variations in each person's response to medications. Current research has revealed that many of the plants used in Ayurveda have substantial anticancer properties. Several such herbs' specific antiproliferative activities have also been investigated. For instance, studies on the association between structure and activity have shown that the many extracts of ashwagandha such as withanolides can interact negatively with various sorts of proteins that are involved in the development of cancer (Tewari et al., 2022).

Similarly, Triphala, a combination of 3 different herbs exhibited the potential to lessen the rapid multiplication of cancer cells by targeting the protein complexes that facilitate cell division such as microtubules (Cheriyamundath et al., 2018). In addition to Ayurveda, a number of other medicinal plants with rehabilitative are utilized in various oriental and western herbal therapies are also being investigated. The efficient implementation of numerous ayurvedic herbs and their extracts to the tumor site is still a difficult process, despite the fact that they are potential antiproliferative agents. Triphala or ashwagandha phytochemical coatings added to formulations exhibit significant antiproliferative effects against cancer cell lines (Meher et al., 2022). A prospective therapeutic agent that can also act as a carrier for equally or more potent pharmacological molecules is referred to as a pharmaceutical (the Greek word phéro means "to carry"). The anticancer modes of these pharmaceuticals have also been reported many times. For instance, it has been demonstrated that gold nanoparticles coated with extract of ashwagandha as well as triphala specifically target different microtubules which are primary proteins of the cytoskeleton that resemble a thread and are necessary for the regulation of cell division. These cytoskeletal proteins/microtubules are primarily involved in the duplication of chromosomes into the in-daughter cells by reconfiguring them into the shape of a mitotic spindle. Cancer treatment has been proven to target microtubules and tubulin, the proteins that makeup microtubules. It has been discovered that these nanomaterials have significant antitumor activity against prostate, lung, and colon malignancies (Sandhya et al., 2006).

Other ayurvedic medicines against cancer

Taxanes are tremendous anti-cancer biomolecules which are documented to demonstrate cytotoxic effects against different kinds of cancerous cells. In native American tribes, several species of Taxus have been used in ayurvedic practices against cancer. Paclitaxel (Taxus) is approved by drug regulatory authorities in different countries against breast as well as ovarian cancers (Wheeler et al., 1992).

Different sorts of flavonoids are used in the ayurvedic medicine system against cancer, for instance, flavopiridol (precursor of rohitukine) is documented to substantially inhibit cyclin-dependent kinases such as CDK1, CDK2, CDK4, and CDK7 (Ali et al., 2009; Mohanakumara et al., 2010). Trials on flavopiridol are ongoing due to its marvelous anti-cancerous activities against pulmonary, breast, head, and neck cancers (Phelps et al., 2009; Shindiapina et al., 2014). Turmeric also referred to as curcumin is a hydrophobic polyphenol chemical which is extracted from the plants of Curcuma longa (Anand et a., 2007). Apart from curcumin, demethoxycurcumin (DMC) and bisdemethoxycurcumin (BDMC) have also been shown turmeric's main ingredients by phytochemical analysis (Himesh et al., 2011). Furthermore, curcumin as well as its derivatives showed exceptional anti-cancerous potential against different types of carcinomas such as duodenal, colon, stomach, and breast carcinoma (Shankar et al., 2008). Owing to the lack of side effects and efficient target potential, it is regarded as a potential chemopreventive and anticancer drug (Shankar & Srivastava 2007). *Calotropis procera* root extract is used against mammary tumors in canines. It is reported that administration of *Calotropis procera* root extract down-regulates the expression of Bcl-2 as a result of proke apoptosis in neoplastic cells thus preventing the proliferation of tumor cells and therefore considered as a potential traditional medicine against mammary tumors of canine (Vahidi et al., 2021).

CONCLUSION

Ayurvedic medicines have been used for centuries as a traditional medicine in India and other parts of the world. Although it is not a replacement for conventional cancer treatments, Ayurvedic medicine has been found to have potential benefits in supporting cancer patients. Some Ayurvedic herbs and treatments have been shown to have anti-cancer properties and may be used as complementary therapies alongside conventional treatments. However, more research is necessary to assess the effectiveness of Ayurvedic medicines in treating cancer.

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