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A review of traditional anticancer nano-medicine: triphala

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Abstract

Ayurveda, the science of life, prevention and longevity is the oldest and most holistic medical system available. In the last few years there has been an exponential growth in the field of herbal medicine and these drugs are gaining popularity both in developing and developed countries because of their natural origin and less side effects. Many traditional medicines in use are derived from medicinal plants, minerals and organic matter. The World Health Organization (WHO) has listed 21,000 plants, which are used for medicinal purposes around the world. It has recently come to the attention of western medical researchers seeking novel therapeutic compounds. The present study was performed to evaluate, the anti-cancer herbal drug (Triphala) preparations. The screening a number of traditional Vedic formulas scientists discovered that one of the most revered of all Ayurvedic combination - Triphala (Harad, Bahada & Amala) in different ratios exhibits a number of health benefits, including: Anti-cancerous, Antipyretic, Antiulcer, Antidiabetic etc. activities.

Keywords: Triphala, Anti-cancer, Antiulcer, Anti-diabetic etc.

1. Introduction

Ayurveda, the science of life, prevention and longevity is the oldest and most holistic medical system available. It is known to have evolved over thousands years ago in the far reaches of the Himalaya in India from the deep wisdom of spiritually enlightened prophets, the Rishis. Their wisdom was transmitted orally from teacher to disciple, and eventually set down in Sanskrit poetry known as the Vedas. Before the advent of writing, the ancient wisdom of healing, prevention and longevity was a part of the spiritual tradition of a universal religion. When world is burning for the cure of a giant cancer disease the Indian well known medicine used since our ancient period (Vedas) as a tonic is the ray of hope. When we are going in the 21st century but today no permanent treatment of cancer available.

Herbal care or traditional system of medicine are used throughout the world and from century's herbs have been the original source for most of the drugs. Medicinal plants contain so many chemical compounds which are the major source of therapeutic agents i.e. active phyto-chemical ingredients (API) to cure human diseases. Recent discovery and advancement in medicinal and aromatic plants have lead to the enhancement of health care of mankind. Various medicinal plants like Neem, Arjuna, Ashwagandha, Tulsi, etc. traditionally used for treating fever. The combination of three medicinal fruits is triphala used in many diseases and cure the effectively the cancerous part in human and animal body. Our ancestors did used this medicine since old ages and were free from cancer and other like death cause.

Triphala is an old Ayurvedic herbal formula prepared by three plants: Haritake (Harad) Bibhitaki (Bahada) and Amalki (Amla). Triphala has antioxidant properties and is promoted as an herbal combination for good digestion. Triphala has historically been used as a digestive aid for constipation. Triphala triggered the cancerous cells to die off and significantly reduced the size of the tumours.



Triphala

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Amala or Amalaki (*Emblica officinalis*)



Harad/Haritaki (*Terminalia chebula*)



Baheda/Bibhitaki (*Terminalia belerica*).

Table 1: Triphala phytochemicals and theruptic uses described in Ayurvedic literature

Sanskrit/Hindi Name (English) Botanical	Phytochemicals ^[13]	Theruptic effect ^[5, 13]
Amalaki /Amala (Emblic Myrobalan) <i>Emblica officinalis</i>	Vitamin C, Nicotinic acid, Tannins, Gallic acid, Ellagic acid, Linoleic acid, Linolenic acid, Oleic acid.	Diabetes, Hysteria, Jaundice, Eczema, Piles, Diarrhoea, Menorrhagia, Scurvy, Rebuilds and maintains new tissues and increases red blood counts,
Bibhitaki /Baheda (Belliric Myrobalan) <i>Terminalia belerica</i>	}-sitosterol, gallic acid, Ellagic acid, Chebulic acid, Mannitol, Oxalic acid, Galloyl, Galactose, Fructose.	Cough, Asthma, Anorexia, Vomiting, Arthritis, Throat disorder, Fever, Epilepsy, Splenomegaly, Piles, Diarrhoea, Leprosy, Brain tonic and laxative.
Haritaki /Harad (Chebulic Myrobalan) <i>Terminalia chebula</i>	Tannic acid, Gallic acid, Chebulinic acid, Anthraquinone, phosphoric acid, Succinic acid.	Constipation, Haemorrhoid, Skin disease, Asthma, Dysentery, Uterine debility, Anaemia, Diabetes, Leucoderma, Tumors and Heart disease.

1.1 Definition of Cancer

Cancer is a term used for diseases in which abnormal cells divide without control and are able to invade other tissues. Cancer cells can spread to other parts of the body through the blood and lymph systems. Cancer is not just one disease but many diseases. There are more than 100 different types of cancer. Most cancers are named for the organ or type of cell in which they start. Cancer types can be grouped into broader categories. The main categories of cancer include:

- 1. Carcinoma** - cancer that origins in the skin or in tissues that line or cover internal organs.
- 2. Sarcoma** - cancer that begins in bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue.
- 3. Leukemia** - cancer that starts in blood-forming tissue such as the bone marrow and causes large numbers of abnormal blood cells to be produced and enter the blood.
- 4. Lymphoma and myeloma** - cancers that begin in the cells of the immune system.
- 5. Central nervous system cancers** - cancers that begin in the tissues of the brain and spinal cord.

1.2 How Cancer Starts

All cancers begin in cells, the body's basic unit of life. To understand cancer, it's helpful to know what happens when normal cells become cancer cells. The body is made up of many types of cells. These cells grow and divide in a controlled way to produce more cells as they are needed to keep the body healthy. When cells become old or damaged, they die and are replaced with new cells. However, sometimes this orderly process goes wrong. The genetic material (DNA) of a cell can become damaged or changed, producing mutations that affect normal cell growth and division. When this happens, cells do not die when they should and new cells form when the body does not need them. The extra cells may form a mass of tissue called a tumor. The effect on DNA is called nano effect.

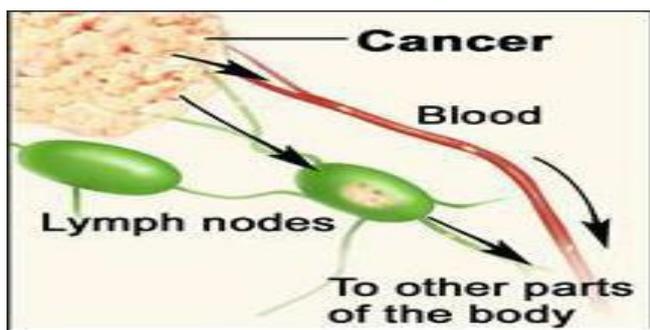


Fig 1: spreading of metastatic cancer cells invade lymph vessels and blood vessels

1.3. Site of Cancer Development in Human body:

The most common sites of cancer metastasis are the lungs, bones, and liver. Although most cancers have the ability to spread to many different parts of the body, they usually spread to one site more often than others. The following table shows, in descending order from left to right, the three most common sites of metastasis, excluding lymph nodes, for several types of cancer:-

Cancer type	Main sites of metastasis
Breast	Lungs, liver, bones

Colon	Liver, peritoneum, lungs
Kidney	Lungs, liver, bones
Lungs	Adrenal gland, liver, lungs
Melanoma	Lungs, skin/muscle, liver
Ovary	Peritoneum, liver, lungs
Pancreas	Liver, lungs, peritoneum
Prostate	Bones, lungs, liver
Rectum	Liver, lungs, adrenal gland
Stomach	Liver, peritoneum, lungs
Thyroid	Lungs, liver, bones
Uterus	Liver, lungs, peritoneum

In local invasion cancer cells invade nearby normal tissue. In extravasation cancer cells invade and move through the walls of nearby lymph vessels or blood vessels. In circulation cancer cells move through the lymphatic system and the bloodstream to other parts of the body [7].



Various kind of drugs play very important role in human life.

Some Chemotherapeutic medicines are used for cancer treatment [8].

- Taxanes: paclitaxel
- Dacarbazine and temozolomide
- Thiotepa and altretamine
- Cladribine, Clofarabine, Cytarabine
- Pentostatin Thioguanine
- Daunorubicin
- Doxorubicin
- Epirubicin
- Idarubicin etc.

1.4 Impurity how damage the DNA this HIV Drug Viracept (DNA damage)

11 Sep 2007 Drug Company Pfizer Inc together with the US Food and Drug Administration (FDA) warned yesterday, Monday, that its HIV drug Viracept (nelfinavir mesylate) may be contaminated with a potential carcinogen and asked doctors not to start pregnant women or children on the drug. Children who are already on the drug and are stable may continue to take Viracept, but pregnant women should be switched to an alternative antiretroviral said Pfizer and the FDA. The drug company issued a Dear Healthcare Professional letter about the presence of an impurity, ethyl methanesulfonate (EMS), that has entered the Viracept formula during the manufacturing process. The letter also gives guidelines on the use of Viracept in pediatric patients and pregnant women. Although no human studies exist, EMS is considered a potential human carcinogen: animal

studies indicate it to be teratogenic (causing birth defects), mutagenic (causing mutation through DNA damage) and carcinogenic (causing cancer). In the meantime the FDA has asked Pfizer to limit the amount of EMS in its US [9].

1.5 Effect of Chemotherapy on immunity

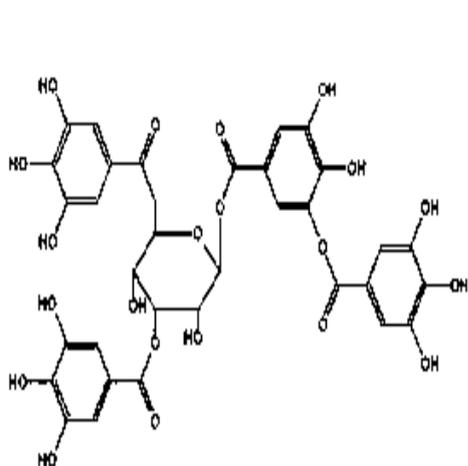
Chemotherapy can make patient more likely to get infections. This happens because most anticancer drugs affect the bone marrow, making it harder to make white blood cells (WBCs), the cells that fight many types of infections [7].

1.6 Ayurvedic herbal formula Triphala

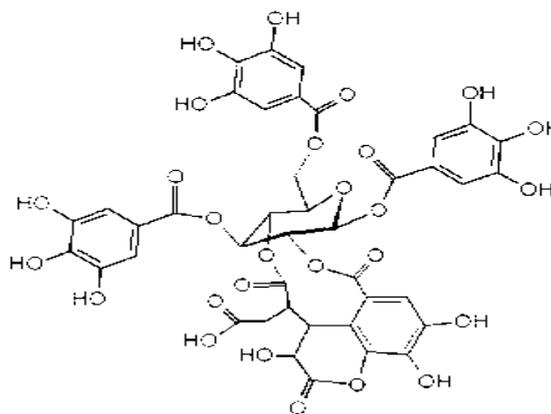
Cancer is an abnormal malignant growth of body tissue or cell. A cancerous growth is called a malignant tumor or

malignancy. The process of cancer metastasis is consisting of series of sequential interrelated steps, each of which is rate limiting. Plants with chemical contains chemo protective activities of some of them are undergoing clinical trial. Inhibition of angiogenesis is a novel process of cancer therapy. The selected and careful use of this plant combination may definitely in anti-angiogenic therapy and thus in cancer management. Triphala is commonly used in Ayurvedic medicine to treat variety of diseases; however its mechanism of action remains unexplored. This study elucidates the molecular mechanism of Triphala against human cancer in the cellular and *In vivo* model.

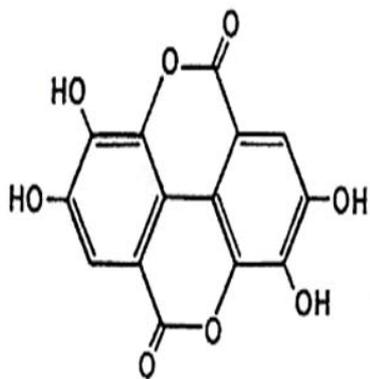
1.7 Some anticancer Phytochemicals [10]



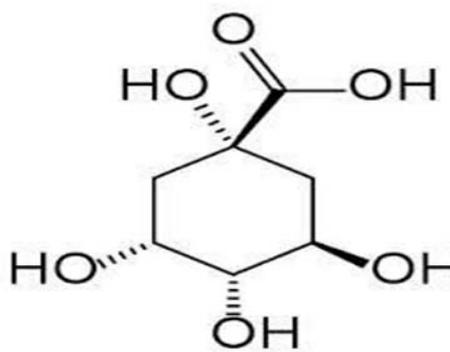
Tannic acid



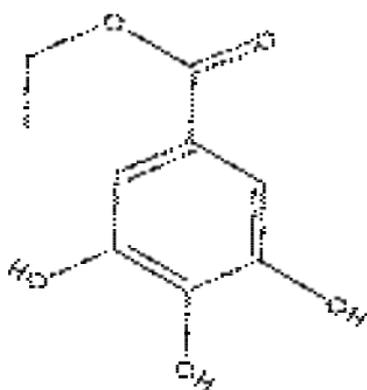
**Chebulinic Acid
(CAS No 18942-26-2)**



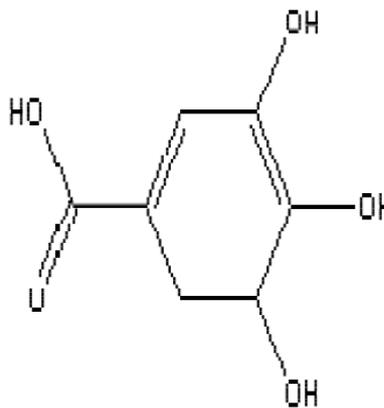
Ellagic Acid



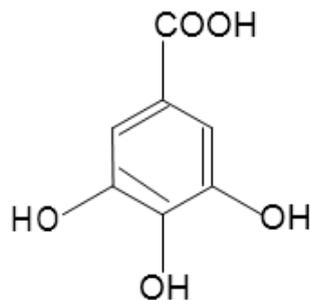
Quinic acid



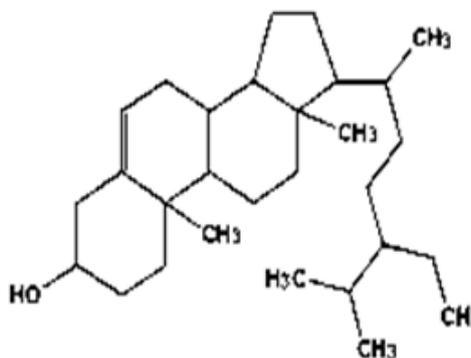
Ethyl galate



Shikimic acid



Gallic acid

*B*-Sitosterol

The phytochemicals found in the triphala are of medical importance to cure the diseases. In the modern system of medicine all drugs are synthetic and have lot of side effects in the human and animal body. The chemical investigations have found that triphala have a lot of chemical compounds to cure the cancer and ulcerous cells in human body. Some of the phytochemical structures have given above shows medicinal properties are as follows- Beta-sitosterol, gallic acid, ellagic acid, ethyl gallate, galloyl glucose, chebulagic acid. Gallic acid biological activities of gallic acid include: Analgesic, Anti-inflammatory, And Antioxidant, Ellagic acid: Ellagic acid is a phenolic compound and known to inhibit certain **carcinogen-induced cancers** and may have other chemo-preventive properties. The effects of ellagic acid on cell cycle events and apoptosis were studied in cervical carcinoma cells ^[11].

1.8 Elemental Contents in Triphala

The presence of elemental contents is suggests that triphala as a whole is rich in Mg, K, Ca, Fe, and Zn, though Se (Selenium) is also present in significant amounts. There appears to be an association between Se deficiency and protein malnutrition disease, multiple sclerosis, cancer and heart disease. It has been suggested that Se (Selenium) as glutathione peroxidase inhibits the replication of tumour viruses and prevents the malignant transformation of cells ^[12]. The triphala and its three constituents have shown V content in the range 1-2 $\mu\text{g/g}$, which has been suggested to play vital role in the treatment of cancer and diabetes ^[13].

2. Discussion

Triphala is novel dietary or natural chemopreventive formulation. Triphala has been used for centuries in Ayurvedic medicine to treat various types of gastrointestinal-related disorders; however, the molecular mechanisms of triphala have not been studied yet. In the present studies, it has demonstrated that aqueous extract of triphala is effective in inhibiting the growth of pancreatic cancer cells in culture as well as in the *In vivo* model. The results reveal that Triphala treatment drastically reduces the survival of Capan-2 and BxPC-3 human pancreatic cancer cells in a dose-dependent manner. On the other hand, Triphala failed to cause any cytotoxic effects on the growth of HPDE-6 near normal pancreatic epithelial cells. Suppression of pancreatic cancer cell growth by Triphala in studied model was due to induction of apoptosis, which in

turn was associated with generation of ROS. Pretreatment of Capan-2 cells with antioxidant NAC blocked ROS generation and completely protected the cells from Triphala-induced apoptosis. The results also demonstrate that Triphala treatment caused DNA damage resulting in the activation of ATM and ERK leading to stabilization. Blocking ERK activation by MEK-1/2 inhibitor U0126 or p53 activation by pifithrin-*a* completely protected Capan-2 (wild type p53) cells from Triphala-induced apoptosis. Similarly, U0126 treatment blocked Triphala-induced apoptosis in BxPC-3 (mutated p53) cells, suggesting ERK as a molecular target of Triphala in pancreatic cancer cells. Further, orally feeding 50 mg/kg or 100 mg/kg Triphala to nude mice significantly retarded the growth of Capan-2 pancreatic tumor xenograft. Tumors from Triphala treated mice demonstrated increased apoptosis in the tumor cells, which was due to the activation of ERK and p53. To the best of our knowledge, this is the first study to report the molecular mechanism of the chemotherapeutic effects of Triphala against pancreatic cancer.

Reactive oxygen species (ROS) are the known mediators of intracellular signaling cascades. Excessive production of ROS nonetheless leads to oxidative stress, loss of cell function and apoptosis or necrosis 14-17. Our results reveal that Triphala-induced apoptosis in pancreatic cancer cells is initiated by ROS generation, the effect of which can be blocked by antioxidant NAC. Several previous studies including those from our laboratory have implicated ROS as a possible mechanism for DNA damage and induction of apoptosis ^[15, 17, 18]. DNA damage plays a critical role in maintaining genomic integrity. Tumor cells exhibit genetic instability causing functional inactivation of p53 that plays an important role in DNA damage checkpoint pathways. In response to DNA damage, p53 is stabilized through phosphorylation at Ser 15 by ATM 19-21. The effects of Triphala are compatible with this assertion. The results do indicate that Triphala treatment causes DNA damage as depicted by increased phosphorylation of H2A.X at Ser 139, an indicator for the presence of DNA double-strand breaks.

Pancreatic tumor growth inhibition and induction of apoptosis *In vivo* was observed by the oral administration of 50 mg/kg or 100 mg/kg Triphala 5 times a week the results were consistent with previous studies where Triphala was shown to be effective in suppressing the growth of Barc-95 (mouse thymic lymphoma) xenograft in mice ²². Although,

pharmacokinetics of Triphala in humans has not been determined, it has been used safely for centuries in the Ayurvedic medicinal system in India for the treatment of various gastrointestinal-related disorders. The effective dose of Triphala in our animal model for suppressing tumor growth, if extrapolated to humans ranges from 4 to 8 grams per day for a person weighing 70 kg. These doses of Triphala come within the dose range already being used by humans in countries such as India.

Triphala churna is a powdered preparation of three myrobalan fruits, *Embllica officinalis* (Amla), *Terminalia chebula* (Haritaki) and *Terminalia belerica* (Bibhitaki) in equal proportions. This fruit formulation has been extensively used in the traditional Indian system of medicine, Ayurveda for the treatment of several disorders of the gastrointestinal and cardiovascular systems [23-26]. In addition, THL is also consumed by the people of Indian subcontinent for its high nutritional value [26]. Recently, it has been demonstrated that THL can inhibit the growth of carcinogen induced stomach cancer, murine thymic lymphoma and human pancreatic cancer in mice. However, there is no mention in these reports regarding the effects of THL on tumor angiogenesis [25-28].

High performance liquid chromatography (HPLC) has revealed gallic acid (GA), ellagic acid (EA) and chebulinic acid (CI) to be the major constituents of THL [24, 26]. The plasma levels of GA and EA after oral intake of fruits containing these two compounds, and thereby their bioavailability has been reported to be poor [29]. As THL has been shown to inhibit malignant tumor growth in animals [25-28], therefore there is a possibility that other bioactive compounds present in THL mediate its anti-tumor effects in these animals.

The cytotoxic effects of aqueous extract of Triphala, an ayurvedic formulation, were investigated on human breast cancer cell line (MCF-7) and a transplantable mouse thymic lymphoma (barcl-95). The viability of treated cells was found to decrease with the increasing concentrations of Triphala. On the other hand, treatment of normal breast epithelial cells, MCF-10 F, human peripheral blood mononuclear cells, mouse liver and spleen cells, with similar concentrations of Triphala did not affect their cytotoxicity significantly. The drug treatment was found to induce apoptosis in MCF-7 and barcl-95 cells *in vitro* as determined by annexin-V fluorescence and proportion of apoptotic cells was found dependent on Triphala concentration. MCF-7 cells treated with Triphala when subjected to single cell gel electrophoresis, revealed a pattern of DNA damage, characteristic of apoptosis. Studies on Triphala treated MCF-7 and barcl-95 cells showed significant increase in intracellular reactive oxygen species (ROS) in a concentration dependent manner. ROS increase was, however, found to be insignificant in MCF-10 F as well as in murine spleen and liver normal cells. *In vivo*, direct oral feeding of Triphala to mice (40 mg/kg body weight) transplanted with barcl-95 produced significant reduction in tumor growth as evaluated by tumor volume measurement. It was also found that apoptosis was significantly higher in the excised tumor tissue of Triphala fed mice as compared to the control, suggesting the involvement of apoptosis in tumor growth reduction. These results suggest that Triphala possessed ability to induce cytotoxicity in tumor cells but spared the normal cells. The differential effect of Triphala on normal and tumor cells seems to be related to its ability to

evoke differential response in intracellular ROS generation. The differential response of normal and tumor cells to Triphala *in vitro* and the substantial regression of transplanted tumor in mice fed with Triphala points to its potential use as an anticancer drug for clinical treatment [3].

The presence of elemental contents is suggests that triphala as a whole is rich in Mg, K, Ca, Fe, and Zn, though Se (Selenium) is also present in significant amounts. There appears to be an association between Se deficiency and protein malnutrition disease, multiple sclerosis, cancer and heart disease. It has been suggested that Se (Selenium) as glutathione peroxidase inhibits the replication of tumour viruses and prevents the malignant transformation of cells [30]. The triphala and its three constituents have shown V content in the range 1-2 µg/g, which has been suggested to play vital role in the treatment of cancer and diabetes [31].

In the recent past, there has been growing interest in exploiting the biological activities of different ayurvedic medicinal herbs, owing to their natural origin, cost effectiveness and lesser side effects [32, 33]. Triphala is one of the ayurvedic medicinal herbal formulations prescribed by most health care practitioners. It is used as colon tonic, laxative, eye rejuvenator, anti-inflammatory, anti-viral etc. Triphala is gentle for people of all ages, from children to seniors and hence is recommended for everybody [34]. Triphala has been tested as an antioxidant and also as a radioprotector in mice [25, 35]. In the recent study, it is tested the *in vitro* antioxidant activity under γ -radiation induced conditions. In order to understand the factors responsible for the antioxidant and radio protection activity, free radical reactions and phytochemical analysis of triphala were carried out.

3. Conclusion

The rapid increase in utilization of herbal remedies worldwide has been inspired by several factors, including the concept that herbal products are safe and effective and so investigation on medicinal plants is increasing day by day. *Triphala* is known as the mother of medicine as it has a biodiversity of both nutritional as well as medicinal components. It is suggested that any herb or plant ingredients taken must be tested before being used as a remedy. Therefore, from this study, it is clear that the medicinal plants play a vital role against various diseases. Triphala has an antiulcer, Antipyretic, Anti-diabetic and Anti-cancerous activity in different animal models. Hence the review study is concluded that the triphala possesses antiulcer, anti-cancerous activity and it has been proved by different animal models which give many links to develop the future trials. The ill community gets maximum benefits from traditional system of medicine. Hopefully, this review will encourage more awareness towards research and more confidence towards utilization of herbal medicines. It will be a link between science and men.

4. Acknowledgements

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