

Interventional role of Haridra (*Curcuma longa* Linn) in cancer

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ABSTRACT

Haridra (*Curcuma longa* Linn (Zingiberaceae family)) is a rhizomatous household spice and has been a widely used herb in India since ancient times. Ayurvedic pharmacodynamics of *C. longa* are described as follows: Rasa – *tikta and katu*, Guna – *ruksha and laghu*, Virya – *ushna*, Vipak – *katu* and *Doshaghnata* – *tridoshshamak*. It is used as a tonic, carminative, antidiarrheal, hepatoprotective and as a purifying agent. It is also used in cancer management. Since years, *haridra* has been used as a hemostyptic agent. However, the oncopreventive aspect of *haridra* has drawn the scientists towards it. Use of *haridra* in *medoja arbuda* is documented in Sushrut Samhita. Recently, it has been found that chronic inflammation has played a role in cancer formation. The kapha and vata shamaka property is responsible for the shothghna activity of *haridra*. Several studies have also proved the anti-inflammatory condition of *haridra*. The essential oil, containing ar-turmerone, as a major component has been shown to possess anti-inflammatory effect of *haridra*. Experimental studies 'in vitro and in vivo' in diverse models have also proved the anti-tumor activity of *haridra*. Curcumin, the chief ingredient, of it is mainly responsible for anticancer property. However other constituents like Turmerone and polysacchrides also play a major role in anti cancer activity. The free radical scavenging activity as well as inhibition of lipid peroxidation by curcumin has been reported by Kuttan *et al*. The mechanisms underlying the anticancer potential of curcumin are complex. Many reports in literature mention about that work carried out regarding the suppression of proliferation of cells of different tumors. They include the down regulation of transcription factors, inhibiting COX2, LOX, inducible nitric oxide synthase, matrix metalloproteinases 9, cell adhesion molecules along with TNF- α . Curcumin inhibits TNF- α -induced AKT activation whereby levels required for NF κ B gene expression are suppressed. Curcumin suppresses the tumor angiogenesis resulting in regression in the tumor metastatic growth. Goel *et al*. have shown the inhibition of expression of COX2 in human colon tumor cell line (Vaidya *et al.*). Kuttan *et al*. showed that the ethanol extract of turmeric as well as the ointment of curcumin produced remarkable symptomatic relief in 62 patients with external cancerous lesions. Scientists at institute of cytology and preventive oncology (ICPO) based in Noida, UP, have found that curcumin protects body from HPV that is one of the primary causes of cervical cancer. Bhide *et al*. showed the therapeutic effect of turmeric oil and turmeric oleoresin on oral submucous fibrosis (SMF) patients. At MRC KHS, a cervical cancer prevention study was approved by an independent ethics committee. The primary objective was to see whether administration of oral turmeric oil for a period of 12 weeks, resulted in the arrest or regression of the premalignant condition, LGSIL, i.e. low grade squamous intraepithelial lesion as detected by Pap smears during the therapy period. It was observed that the lesion in Pap smears was arrested in 3/19 cases and regressed in 16/19 cases (Joshi *et al*, Asian Pac J Cancer Prev 2011). Experimental data suggest that curcumin acts at each stage of promotion, progression, and metastasis of cancer. *Haridra* which has anticancer potential, can be considered as complementary medicine for cancer treatment as well as prevention.

Key words: Cancer, chemoprevention, curcumin, *haridra*

INTRODUCTION

Plants have always been an important source of medicine

since ages. They were used first in aboriginal or folk medicine and later adopted by conventional Western medicine, as their efficacy was confirmed. The evolution from folk remedy to pharmaceutical agents has followed a path which was brought about by the merger of medicine and science. It is logical to revisit and revive the age-old medicines for the welfare of mankind. Cancer is one absolute enemy of mankind where the majority of chemotherapeutic agents have adverse side effects. Although there are plant-based chemotherapeutic agents such as taxol and vincristin reported to have anticancer effects, they render equally grave side effects. Hence we are bound to look for safe chemopreventive alternatives.

Access this article online

Quick Response Code:



Website:

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DOI:

10.4103/2278-0513.99556

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There is growing evidence that populations with greater reliance on fruits and vegetables in the diet experience a reduced risk for the major cancers.^[1]

Haridra is one such product. It is a part of our daily food habit, and its use in large quantities from ancient time has already proved that it is a safe product. The major classes of phytochemicals with disease-preventing functions are antioxidants, detoxifying agents, and immunity-potentiating agents. Such dietary phytochemicals include curcumin (diferuloylmethane), a major naturally occurring phenolic compound, obtained from the rhizome of the plant *haridra* (*C. longa*). In fact, curcumin preferentially induces apoptosis in highly proliferating cells; cellular death is much more pronounced in tumor cells than normal ones.^[2]

Taken together, this study seeks to summarize the unique properties of *haridra* that may be exploited for successful clinical cancer prevention.

HARIDRA IN AYURVEDIC CLASSICS

Its history goes back over 3000 years to the heyday of ayurveda. From the time of *Atharvaveda*, *haridra* is being used as a medicine for mankind. It was formed at night so-called *rajani*. It is stated in *Atharvaveda* that turmeric is to be used for skin disorders especially for black spots on the skin. All poisons can be removed from the body if treated with the paste of turmeric (*Mastyā purana* 218, 20 (eighth century AD)).

Ayurvedic classics have also described several uses of *haridra*. The sanskrit word *haridra* literally means that the one which improves the complexion of the skin. It is popularly known as *haldi* (turmeric). It is an integral part of the Indian cuisine and is also used in Hindu religious functions, wedding, and festivals since centuries. In ayurvedic texts, it has various synonyms describing its virtues like *kanchani* – which renders golden tinge to the skin, *nisha* which is beautiful like a night, *harita* – yellow, *varavarnini* of excellent colour, *varnadayi* – which imparts better color to the skin, etc. It has been praised as the drug of choice in the treatment of diabetes (*meheshu dhatri nisha*). The great sage Charaka has categorized it as *lekhaniya* – a scrapping herb, *varnya* – complexion improving herb, *vishaghna* – anti-toxin and *kusthaghna* – anti-dermatosis. Susruta has classified it under *stanyasodhaka* – lactodepurant. Many ayurvedic texts have also categorized it as *kandughna* – anti-pruritic, *kamlanashaka* – alleviating jaundice, *vranaopaka* – wound healer, *sonitasthapaka* – styptic and *shirovirechak* – cleansing nasal therapy.^[3]

Curcuma domestica, *Triticum sativum* and *Symplocos racemosa* were powdered mixed with honey and applied to *Medoja arbuda*.^[4]

Haridra possesses *jwaraghna* property (Vishwanath Dwivedi). The *jwaraghna* (anti-pyretic) property should also be looked up as spontaneous regressions have been reported, in cancer patients with fever, infections, and bacterial lipopolysaccharoides. It is worthwhile to investigate whether in fever and infections, the oncopreventive components of *haridra* gets enhanced.

Ayurvedic properties of *C. longa* are described as follows: *Rasa* – *tikta* and *katu*, *Guna* – *ruksha* and *laghu*, *Veerya* – *ushna*, *Vipaka* – *katu* and *Doshaghata* – *tridoshshamak*.

The *kapha* and *vata shamaka* property is responsible for the *shothaghna* activity of *haridra*. Several studies have also proved the anti-inflammatory condition of *haridra*.^[3] Turmeric was also mentioned in the writings of Marco Polo describing his journey to China and India in 1280 AD and it was first introduced to Europe in the 13th century by Arab traders.

C. longa Linn (Zingiberaceae family) has been widely used in India since ancient times. It is a short-stemmed perennial, which grows to about 100 cm in height. It has curved leaves and oblong, ovate, or cylindrical rhizomes. *C. longa* grows naturally throughout the Indian subcontinent and in tropical countries, particularly South East Asia. A traditional remedy in “ayurvedic medicine” and ancient Indian healing system that dates back over 5000 years, turmeric has been used through the ages as an “herbal aspirin” and “herbal cortisone” to relieve discomfort and inflammation associated with an extraordinary spectrum of infections and autoimmune diseases.^[5]

PHYTOCONSTITUENTS

C. longa contains 2.4% of pigments called curcuminoids and 3.8% essential oil containing different sesquiterpenes. The curcuminoids include curcumin along with two other congener's demethoxycurcumin and bisdemethoxycurcumin; these are diarylheptanoids with different substituents. Curcumin was isolated in 1842 by Vogel, in 1910 Milobedzka determined the structure, in 1918 Lampe substantiated structure by synthesis, and in 1953 Srinivasan showed natural curcumin to be a mixture.^[6]

Curcumin is not soluble in water but soluble in dimethylsulfoxide, acetone, and ethanol and in oils. Curcumin gives maxima at 420 nm in UV spectra. Curcumin p.o. gives curcumin glucuronide and curcumin sulphate as major metabolites; when administered intraperitoneal it gives tetrahydrocurcumin, hexahydrocurcumin, and hexahydrocurcuminol.

The rhizomes and leaves, on hydro distillation, give

essential oils – 3.8% and 1.32%. The major sesquiterpenes are α -turmerone, β -turmerone, ar-turmerone, ar-curcumene, zingiberene, α -phellandrene, and 1,8 Cineole along with other minor components. Supercritical CO₂ extraction gives high yield of the lipophilic extract containing all the essential oils without any degradation and without any solvent residues. Four polysaccharides – ukonans, A, B, C and D, are isolated from the rhizomes. All these ukonans exist in addition to a small amount of peptide moieties. Phenolic sesquiterpenic alcohols, turmenol A and B, have been isolated. A novel water soluble peptide – turmerin – has been isolated and studied.^[7]

THERAPEUTIC ACTIVITIES OF HARIDRA

Anti-inflammatory activity

Inflammation is known to play a major role in the development of most diseases including cardiovascular disease, pulmonary diseases, neurological diseases (including Alzheimer's), autoimmune diseases, arthritis and diabetes and cancer.^[8]

Most of the anti-inflammatory activities of curcuma have been carried out on carrageen-induced edema in rats and mice.^[9-11] Petroleum ether extract, water, and alcohol extracts of *C. longa* have also shown anti-inflammatory effects. The essential oil, containing ar-turmerone, as a major component has shown to possess anti-inflammatory activity.^[12] Ar-turmerone is anti-mutagenic in nature and anti-platelet activator. It potentiates antioxidant activity of curcuminoids.^[13]

When we talk about inflammation the term NF κ B (nuclear transcription factor kappa beta) comes up, all we need to understand at this point is that NF κ B has a major role in most diseases and inhibition (blocking) of NF κ B can suppress inflammation. Scientists are excited about curcumin because it has been shown consistently to inhibit NF κ B. Curcumin inhibits TNF- α induced AKT activation whereby levels required for NF κ B gene expression are suppressed.^[14]

Cheng *et al.* had prospective Phase I study using biological effective doses of curcumin in humans followed by toxicological and pharmacokinetic studies. Patients ($n = 25$) were given doses of curcumin in the range starting from 500 mg/kg to 12,000 mg/kg orally. There were no adverse events in patients up to the dose of 8000 mg/kg. However, higher doses were unacceptable to the patients. Curcumin was poorly absorbed.^[15]

Satoskar *et al.* have shown that the use of curcumin (400 mg t.d.s) is quite safe and when given with phenylbutazone,

it produced a better anti-inflammatory effect than placebo in 46 patients.^[16]

A study was done by deodhar *et al* on safety and anti-inflammatory activity of curcumin: a component of turmeric (*Curcuma longa*) in patients of rheumatoid arthritis.^[17]

Anticancer activity

A lot of the research into curcumin has focused on cancers. The mechanisms responsible for anti-cancer activity of *haridra* may be through: (1) free radical scavenging activity, (2) blocking of NF κ B, (3) anti-mutagenic activity, and (4) anti-oxidant activity.

Bhide *et al.* have reported the inhibition of nitrosation and anti-mutagenic activity of curcumin against various environmental mutagens *in vitro*.^[18]

The free radical scavenging activity as well as inhibition of lipid peroxidation by curcumin has been reported.^[19] Srinivas *et al.* reported the water-soluble protein turmerin – a polypeptide as an antioxidant.^[20]

According to a cancer researcher Bharat Aggarwal, a professor of cancer medicine, at the MD Anderson Cancer Centre University of Texas, the incidence of the top four cancers in the United States – colon, breast, prostate and lung – is as much as ten times lower in India where significant amounts of turmeric are consumed daily. Prof. Aggarwal says, "We have not found a single cancer on which curcumin does not work". Prof. Aggarwal's hypothesis is that most cancers exhibit activated NF κ B which in turn promotes the proliferation and metastasis of tumors. Blocking of NF κ B suppresses the formation of tumors.^[15]

Ayurvedic formulations having potential for anticancer activity contain several plant-based ingredients. Mechanistically, these may act on different targets and since different formulations may be influenced by multiple pathways. Bhalachandran and Govindarajan have written an excellent review on the medicinal plants used in the ayurveda for anticancer activity; curcuma too is discussed.

Vaidya *et al.* have written an excellent review on complementary and alternative medicine for cancer care in India: basic and clinical perspectives. It describes the anticancer properties of several ayurvedic plants namely *Withania somnifera* (L) Dunal, Syn., *Tinospora cordifolia* (Willd.) Miers, *Semecarpus anacardium* Linn and *C. longa* Linn.^[8]

Sino Vedic Research Centre has developed numerous formulations of *C. longa* along with other medicinal plants. These formulations have shown to be active on cancers of

colon, rectum, lung, larynx, thyroid, urinary bladder, non-Hodgkin's lymphoma, and oral cavity.^[21]

Curcumin suppresses the tumor angiogenesis resulting in regression in the tumor metastatic growth.^[22] Goel *et al.* have shown the inhibition of expression of COX2 in the human colon tumor cell line.^[23]

Curcumin induces apoptosis in cancer cell lines. Anticancer activity of curcumin is activated through apoptosis supported by experimental studies on cell lines.^[24] However, Somasundaram *et al.* have hypothesized that curcumin may interfere with the effects of some of the chemotherapeutic drugs which induce apoptosis through the ROS and JNK pathway.^[25] Mahadey *et al.* have demonstrated inhibition of *Helicobacter pylori* by curcumin in rodents preventing cancer of gastric and colon cancers.^[26] Work carried at Bhavan's SPARC on *in vitro* and *in vivo* bioassay of the curcumin and curcuma extract supports utility of these products in chronic inflammatory diseases such as cancer, diabetes, etc. (unpublished data). Curcumin as well as *C. longa* extract shown cytotoxicity in transplantable rat insulinoma cells. These showed anti-oxidant activity assessed by non-enzymatic ally by NBT (nitro blue tetrazolium salt) assay.^[27]

Kuttan *et al.* showed that the ethanol extract of turmeric as well as the ointment of curcumin produced remarkable symptomatic relief in 62 patients with external cancerous lesions.^[28] The following were noted: reduction in smell in 90% of cases, reduction in itching in almost in all cases, dry lesions in 70% of cases, and 10% patients had a reduction in the lesion size and pain. Only one patient had an adverse event whereas almost all patients had good tolerability for several months.

Sharma *et al.* had treated patients (n=15) with advanced colorectal cancer refractory to standard chemotherapies. These were treated with standard curcuma extract in the proprietary capsule form with 450 mg/kg and 3600 mg/ kg containing 36–180 mg of curcumin, daily up to 4 months.^[29] The tolerability was good. Patients with 450 mg/kg for 29 days observed a 59% decrease in lymphocytic glutathione- S-transferase. Patients treated with radiation along with the curcumin extract for 2–4 months showed stable condition.

Curcumin has been found to be a powerful inhibitor of the Human Papillomavirus (HPV) which is linked with cervical cancer *in vitro*. Data on this were presented at the 24th Annual Convention on HPV and Cervical Cancer in 2005.^[30]

Researchers at MD Anderson Cancer, University of Texas, reported that curcumin could stop the spread of multiple myeloma, head and neck cancer, mantle cell lymphoma, lung cancer, melanoma, pancreatic cancer, prostate cancer, breast cancer and others by triggering apoptosis (programmed cell death).^[31]

Of significant interest to scientists is that curcumin appears to have a therapeutic potential for preventing breast cancer metastasis. In the publication 'Phytopharmaceuticals in Cancer Chemoprevention', Prof. Aggarwal and colleagues have stated when it comes to HER2 positive breast cancers, curcumin down regulates the activity of epidermal growth factor receptor (EGFR) and expression of HER2/neu. The researchers say, "Curcumin depletes cells of HER2/neu protein". If this is true, it has huge implications. A study conducted at Department of Oncology, National Taiwan University Hospital and reported in "Clinical Cancer Research" seems to confirm this. They say, "The erbB2/neu gene (also known as HER-2) encodes a 185-kDa protein that has tyrosine kinase activity. The amount of P185 neu protein on the cell membrane was drastically reduced after curcumin treatment." It is worth noting that the drug herceptin was developed to achieve the same outcome. Prof. Aggarwal was one of the head cancer researchers at Genentech, the company behind Herceptin.^[32]

At MRC KHS, a cervical cancer prevention study has been put up to an independent ethics committee and is approved. The primary objective is to see whether administration of turmeric oil for a period of 12 weeks, results in the arrest or regression of the premalignant condition, LGSIL, i.e. low grade squamous intraepithelial lesion, during therapy period (Joshi *et al.*).^[33]

USE OF HARIDRA AS A COMPLEMENTARY MEDICINE

A clinical study of the role of *Rasayana* as a pre-, adjuvant- and post-treatment of chemotherapy in management of carcinoma was carried out in 50 patients of carcinoma receiving chemotherapy, *Rasayana Avaleha* containing several drugs such as *amalaki*, *guduchi* as well as *haridra* as a *prakshep dravya* was administered in a dose of 10 g bd for 3 months. The effect of therapy was significant on mouth ulcers, constipation, and myelosuppression and on improving general well-being of the patient.^[34]

Effect of Rasayana Avaleha on adverse effects of chemotherapy:

- 46.01% relief was found in the complaints of nausea and vomiting
- 42.32% relief was found in constipation
- 42.02% relief was found in mucositis
- 19.5% relief was found in maintaining the WBC count.

Effect of chemotherapy on patients who were not administered Rasayana Avaleha:

- Nausea and vomiting worsened by 74%
- Constipation worsened by 67.32%
- Alopecia worsened by 19.66%
- Hb fall was by 8.18%
- WBC fall was up to 79.25%

Chemo-preventive activity

Hastak *et al.* reported the alcoholic extract of turmeric (TE), turmeric oil (TO), and turmeric oleoresin (TOR) on the incidence of micronuclei (Mn) in circulating lymphocytes from healthy subjects induced *in vitro* by benzo pyrene. The three modalities of treatment decreased – the number of Mn in both exfoliated oral mucosal cells and in the circulating lymphocytes. The Mn counts with BP were $3.7 \pm 0.8/100$ cells as compared to the control count of 1.5 ± 0.02 . Turmerone and oleoresin reverted the effects of BP to baseline Mn counts.^[35]

SMF of oral mucosa, a precancerous condition, prevails in India because of tobacco chewing and other dietary habits. Earlier studies by investigators at Bhavan's SPARC (support – Chandan family) had shown oncopreventive properties of *C. longa* and its constituents by *in vivo* and *in vitro* experiments. The ICMR supported study has subsequently extended observations in patients with SMF.

A marked improvement in opening of the mouth after treatment with turmeric products in patients suffering from SMF is seen. Simultaneously, a marked reduction in scores of micronuclei in exfoliated buccal mucosal cells was seen in patients after treatment.^[36]

Clinical safety evaluation and organ function tests with turmeric oil (TO) in healthy volunteers showed that the TO was well tolerated and organ safety was established.^[33] Phase I clinical trial of turmeric oil (TO) was designed to study the safety and tolerance of TO in volunteers for a period of 3 months.^[37]

Prevention of metastases

Currently, there is no effective therapy for metastatic breast cancer after surgery, radiation, and chemotherapy have been used against the primary tumor. Because curcumin suppresses NFκB activation and most chemotherapeutic agents activate NF κB that mediates cell survival, proliferation, invasion, and metastasis, we hypothesized that curcumin would potentiate the effect of chemotherapy on advanced breast cancer and inhibit lung metastasis.

Curcumin suppresses the paclitaxel-induced nuclear factor- κB pathway in breast cancer cells and inhibits lung metastasis of human breast cancer in nude mice.^[38]

CONCLUSION

Despite considerable recent advances in securing remission and possible cure, cancer has remained a disease equated with hopelessness, pain, fear, and death. Its diagnosis and particularly the treatment is much painful than the

actual symptoms of the disease. Patients have common fears, which have been called the six D's, Discomfort, Dependency, Disfigurement, Disability, Disruption of relationships, and Death.

Over the past several decades, cancer treatment includes multi modal treatment regimens (surgery, chemotherapy and radiation) and palliative therapy administered by various routes and innovative procedures have added longevity and symptomatic relief in a large number of cancer survivors. However, the quality of life of these survivors during and even after the treatment period is pitiable. At this juncture, following the concept of Integrative oncology drugs like *haridra*, by virtue of its anti-cancer potential, can offer a lot of aid in improving and augmenting the quality of life of cancer patients.

Experimental data suggest that curcumin acts at each stage of promotion, progression, and metastasis of cancer. Curcumin/turmeric can be promoted as a complementary alternate medicine for cancer treatment. It can be used in following aspects:

1. to supplement anti-cancer treatment
2. to reduce pain and complications
3. to reduce side effects of chemotherapy and radiotherapy
4. to prevent metastasis

Besides curcumin and turmeric oil may have chemo-preventive potential. Due to shortcomings of conventional chemotherapy in the advanced stages of cancer and its adverse effects, *haridra* with a defined molecular target approach will play an important role in future in palliative treatment. Its role as a chemopreventive agent will also prevent cancer and thus the number of deaths caused by this disease.

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Cite this article as: Buch ZM, Joshi J, Amonkar A, Vaidya AB. Interventional role of Haridra (*Curcuma longa* Linn) in cancer. *Clin Cancer Investig J* 2012;1:45-50.

Source of Support: Nil, **Conflict of Interest:** None declared.