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Curcumin (The Indian solid gold): A review of anti-cancer potential against colon cancer

Priya Mogra* and Preeti Singh

Department of Zoology, College of Science, Mohal Lal Sukhadia University, Udaipur, India.

Correspondence Address: *Priya Mogra, Department of Zoology, College of Science, Mohal Lal Sukhadia University, Udaipur, India.

Abstract

The current review focuses on the diverse molecular targets modulated by curcumin that contribute to its efficacy against colon cancers. Curcumin, (diferuloylmethane) is a yellow pigment present in the spice turmeric (*Curcuma longa*) polyphenolic constituent, is the most active ingredient in the traditional herbal remedy. Dietary spice turmeric is obtained from the rhizome. It has been associated with over 150 potentially therapeutic activities, including antioxidant, anti-inflammatory, anticancer, antiviral, and antibacterial activities as indicated by many citations. Research has shown curcumin to be a highly pleiotropic molecule capable of interacting with numerous molecular targets involved in inflammation. Based on early cell culture and animal research, clinical trials indicates curcumin may have potential as a therapeutic agent in diseases such as inflammatory bowel disease, pancreatitis, arthritis, and chronic anterior uveitis, as well as certain types of cancer. Because of curcumin's rapid plasma clearance and conjugation, its therapeutic usefulness has been somewhat limited, leading researchers to investigate the benefits of complexing curcumin with other substances to increase systemic bioavailability. Numerous clinical trials in progresses should provide an even deeper understanding of the mechanisms and therapeutic potential of curcumin on colon cancer. As discussed in this review, various scientific reports revealed that curcumin has demonstrated powerful anti-cancer effects in a variety of malignancies via its effects on a host of biological pathways involving a number of transcription factors, growth factors, inflammatory cytokines, protein kinases, and other oncogenic molecules in tumorigenesis and cellular growth. The anticancer activities of curcumin derive from its complex chemistry as well as its ability to influence multiple signalling pathways. Curcumin has shown anti-proliferative effect in multiple cancers, and is an inhibitor of the transcription factor NF-κB and downstream gene products (c-myc, Bcl-2, COX-2, NOS, Cyclin D1, TNF-α, interleukins and MMP-9). The objective of current review is to highlight reports on use of curcumin in treatment of colon cancer and its anti-inflammatory properties.

Keywords: Curcumin, anti-inflammatory, herbal medicine, colon and cancer

Introduction

Colon cancer is considered to be the third most important disease that contributes to significant falalaties all over of the globe. This type of cancer initially begins in intestine and in due course of time spread to other parts of the body resulting in danger to life of affected person. If colon cancer is detected in the early stages, and then we can think of a few natural remedies that will help in treating colon cancer. This will help in preventing individuals from undergoing complicated surgeries as well as radiation treatments relevieng considerable stress and trauma, dietary constituent turmeric is consumed worldwide and is almost daily consumed in India. Turmeric flavouring, colourant, additive of food gives taste to the palate but that addvertantely serves also protect body from several aliments. Curcumin has been attributed to be providing a therapy which is able to cure and prevent colon cancer without any side effects. The most compelling agent that stands out and has emerged as a potent *multimodal* cancer preventing agent, with numerous scientific reports published appearing in the global scientific literature in the past year alone. In this review, research demonstrating curcumin's power to disrupt specific molecular mechanisms that leads to cancer. In adding together, many clinical studies have been carried out with curcumin.

Curcumin is the major active component of turmeric, a yellow compound originally isolated from the plant *Curcuma longa*. It has been used for centuries in traditional medicines as a spice; it provides curry with its distinctive color and flavor.

The primary active constituent of turmeric and one responsible for its vibrant yellow color is curcumin, first identified in 1910 by Lampe and Milobedzka *Curcuma longa* has a long history of use in Ayurvedic medicine as a treatment for various aliments: curcumin (diferuloylmethane) comprised demethoxycurcumin, and bisdemethoxycurcumin, as well as volatile oils (tumerone, atlantone, and zingiberone), sugars, proteins, and resins [1,2]. Furthermore, traditional Indian medicine has considered curcumin a drug effective for various respiratory conditions such as asthma, bronchial hyperactivity, and allergy as well as for other disorders including anorexia, coryza, cough, hepatic diseases, and sinusitis [3,4]. Extensive research over the many years has shown that it plays an important role in the prevention and treatment of various pro-inflammatory chronic diseases including neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and malignant diseases. However, a number of line of evidence indicates that this agent is highly pleiotropic with antioxidant [5], wound healing [6], antimicrobial activities [7], hypoglycemic [8] and anti-inflammatory [9]. Based on early research conducted with cell cultures and animal models, pilot and clinical trials indicate curcumin may have potential as a therapeutic agent in diseases such as inflammatory bowel disease, pancreatitis, arthritis, and chronic anterior uveitis, as well as certain types of cancer [10].

It has been shown to possess chemosensitization, chemotherapeutic and radiosensitization activities as well [11]. This review focuses on one of the best-explored actions, the anti-inflammatory effects of curcumin against colon cancer. Curcumin's multimodal effects act to simultaneously counter discrete causative factors in cancer development. It intervenes at each stage in complex sequence of events that must occur in order for a cancer to develop, progress, invade, and ultimately metastasize to healthy tissue. The multi-targeted mechanisms of curcumin have yielded compelling results in combating a remarkably broad array of cancers, including those of breast, uterus, cervix, prostate, and gastrointestinal tract. A burgeoning body of

research demonstrates curcumin's potential to counter cancers of the blood, brain, lung and bladder as well [12-15]. Curcumin has been studied for its chemopreventive potential in a wide variety of cancers, in both preclinical studies and in clinical trials [16-17]. Because of its credulous properties, curcumin is being marketed in several countries including the United States, India, Japan, Korea, Thailand, China, Turkey, South Africa, Nepal, and Pakistan in different form such as capsules, tablets, ointments, energy drinks, soaps, and cosmetics [18]. Curcumin has been found to suppress initiation, progression, and metastasis of a variety of tumors. These anti-cancer effects are predominantly mediated through its negative regulation of various transcription factors, growth factors, inflammatory cytokines, protein kinases, and other oncogenic molecules. It also abrogates proliferation of cancer cells by arresting them at different phases of the cell cycle or by inducing their apoptosis [19].

The current review focuses on the diverse molecular targets modulated by curcumin that contribute to its efficacy against various human cancers. Curcumin's effect on cancer is also discussed; however, an exhaustive review of its many anticancer property of curcumin is outside the scope of this review.

Colorectal cancer is directly impacted by diet and lifestyle

Colorectal cancer is a food related cancer. Everything ingested passes over lining of digestive tract. The lining of large intestine and rectum at lower end of digestive tube contains waste, digestive fluids, bile acids and fiber. That lining is bathed by chemicals in food, hormones, and secretions, healthy and unhealthy bacteria. The content of intestine has a direct impact on health of tissues. Colorectal cancer is directly impacted by diet. The risk of colorectal cancer increases with age. Most colon cancers are due to old age and lifestyle factors with only a small number of cases due to underlying genetic disorders. Some risk factors include consuming fiberless diet, obesity, smoking, and lack of physical activity [20-21]. Modifiable factors that increase risk include high consumption of red or processed meat, low calcium intake, moderate to heavy alcohol consumption, and very low intake of fruits and vegetables. Consumption of whole grain fiber reduces risk. Some of the main reasons for the development of colon cancer in people are: history of colon cancer in the family, Crohn's disease and colon polyp's formation. Studies show increased levels of inflammation and oxidative stress in colon with diets lacking plant antioxidants. Increased inflammation and low antioxidant levels is an environment that promotes colon cancer [22-23].

A wide variety of whole grains, fruits, vegetables as well as herbs and spices with known as anti-cancer properties. The herbs are used in Ayurveda to bring balance to in immune system and helping to minimize or completely eradicate colon cancer. Reflecting upon curcumin recommendations for dietary choices has been used in both traditional Mediterranean and Asian diets**.** Cultures where traditional diets are still eaten today have been found lower rates of colon cancer such as India than other countries such as the United States and some European countries where a modern diet seems to promote and create higher risk for colon cancer [24-29].Consume curcumin choices seem clear, and pretty tasty for healthy life. So there is urgent need to eat powerful dietary antioxidant such as curcumin substance along with our diet which combats increased levels of inflammation and oxidative stress in the colon. Curcumin which has been attributed with anti-inflammatory and antioxidative properties show strong anti-oxidative activity at neutral and acidic pH.

This activity has been reported to be 10 times more potent than that of vitamin E [30-32].

Global reports of incident case of colorectal cancer

Colorectal cancer (CRC) is an alarming health problem worldwide. Cancer is the second leading cause of death in the US, and the risk of developing the disease increases significantly as we age. According to the American Cancer Society, one out of every three women in the United States risks developing some form of cancer over the course of their lives. For men, that number rises to one in two. Since cancer is an age-related disease, the risk of diagnosis increases the longer one lives, making it the second leading cause of death in U.S. [33-34].

In United States

Howlader *et al*., [35] reported that based on rates from 2007 to 2009, 4.96% of US men and women born today would be diagnosed with colorectal cancer during their lifetime from 2005 to 2009, the median age at diagnosis for cancer of colon and rectum in the US was 69 years of age. Approximately 0.1% was diagnosed under age 20; 1.1% between 20 and 34; 4.0% between 35 and 44; 13.4% between 45 and 54; 20.4% between 55 and 64; 24.0% between 65 and 74; 25.0% between 75 and 84; and 12.0% 85+ years of age. Rates are higher among males (54 per 100,000 c.f. 40 per 100,000 for females) in the United States.

The American Cancer Society's estimated for the number of colorectal cancer cases in the United States for 2016 were: 95,270 new cases of colon cancer and 39,220 new cases of rectal cancer [36].

Lifetime risk of colorectal cancer

American Cancer Society's reported that overall, the lifetime risk of developing colorectal cancer is: about 1 in 21 (4.7%) for men and 1 in 23 (4.4%) for women. This risk is slightly lower in women than in men. Cunningham *et al.,* [37,38] and Lozano *et al.,* (2012) reported that globally more than 1 million people get colorectal cancer every year and resulting in about 715,000 deaths as of 2010 up from 490,000 in 1990 [36] .

Reports of GLOBOCAN, [39] stated that it is the third most common cancer in men (663000 cases, 10.0% of all cancer cases) and the second most common in women (571000 cases, 9.4% of all cancer cases) and the third leading cause of cancer death in both men and women in the US. The result is countless avoidable colon cancer deaths each year in the world.

As of 2012, it is the second most common cause of cancer in women (9.2% of diagnoses) and the third most common in men (10.0%)[40-41] with it being the fourth most common cause of cancer death after lung, stomach, and liver cancer [42].

Ferlay *et al.,* [43] reported that globally incidences vary 10-fold with highest rates in Australia, New Zealand, Europe and the US and lowest rates in Africa and South-Central Asia.

Reports of ACS stated that colorectal cancer death rates have been declining since 1980 in men and since 1947 in women, with an overall drop of 49% from 1976 to 2012. This trend reflects improvements in early detection and treatment, as well as declines in incidence. From 2003 to 2012, death rates declined by 2.8% per year. The American Cancer Society estimated that 136,830 people would be diagnosed with colorectal cancer and 50,310 people would die from the disease in 2014. Almost 60% of cases are encountered in developed countries. The number of CRC-related deaths is estimated to be approximately 608000 worldwide, accounting for 8% of all cancer deaths and making CRC the fourth most common cause of death due to cancer. In India, the annual incidence rates for colon cancer and rectal cancer in men was 4.4 and 4.1 per 100000,

respectively. The annual incidence rates for colon cancer in women were 3.9 per 100000. Colon cancer ranked 8th and rectal cancer ranked 9th among men. For women, rectal cancer did not figure in the top 10 cancers, whereas colon cancer ranked 9th. It is expected to cause about 49,190 deaths during 2016 in United States [36].

In other countries

In the NCRP [44] report, the highest annual incidence rates in men for CRCs was recorded in Thiruvananthapuram (4.1) followed by Banglore (3.9) and Mumbai (3.7). The highest annual incidence rates in women for CRCs was recorded in Nagaland (5.2) followed by Aizwal (4.5). Risk factors for CRC can be broadly divided into genetic and environmental or lifestyle-related factors. Most CRCs are sporadic, although genetic factors increase the risk considerably.

Jess *et al.,* [45] in a population-based study from Denmark, suggested that the risk of colon cancer in ulcerative colitis is not as high as previously reported and in fact may not be different than that in the general population.

Reports on colon cancer treatment by curcumin

Ameliorative potential of curcumin on colonic carcinogenicity has been reported by following scientist and researchers where Azuine *et al.,* [46] reported that dietary administration of curcumin significantly inhibited colon carcinogenesis in mice and rats.

Rao *et al.,* [47] reported that dietary curcumin suppressed azoxzymethane induced colonic preneoplastic lesions and colon tumor incidence and tumor multiplicity.

Rao *et al.,* [48] reported that curcumin had antioxidative, anti-inflammatory and chemopreventive activities. To determine whether aging affected the inhibition of colon carcinogenesis by curcumin, young (6 weeks), mature (12 moths), and old (22 moths) F344 male rats were fed with either 0.6% of curcumin or a control diet. Abberrant cryptic foci (ACF) were induced with two weekly S.C. injections of azoxymethane. After an additional 3 month the diets, the number, multiplicity, and distribution of ACF were evaluated. Addition of curcumin to the diet reduced the number of ACF by 49% in young rats and by 55% in old rats. However, interestingly, no reduction of ACF was found in mature rats fed curcumin. Inhibition of large ACF was also affected by age, with the greatest reduction of large ACF occurring in old rats. However, animal age did not significantly alter the effect of dietary curcumin on reduction of cyclooxygenase-2 m RNA expression in the liver or reduction of serum total cholesterol levels. These results indicated that age may play a significant role in the efficacy of chemoprevention of colon cancer by curcumin. This study was designed to investigate the chemopreventive action of dietary curcumin on azoxymetane-induced colon carcinogenesis and modulate effects of curcumin on the colonic mucosal and tumour phospholopase activities in male F344 rats. The results indicated that the administration of curcumin significantly inhibit colon adenocarcinomas ($p<0.004$) and the multiplicity of invasive, non-invasive total adenocacinomas. Curcumin also significantly suppressed the colon tumor volume by more than 57%, compared to the control diet. Although the precise mechanism by which curcumin inhibited colon tumourigenesis remains to be elucidated, it is likely that the chemopreventive action, at least in part, may be due to the modulation of arachidonic acid metabolism.

Larmonier *et al.,* [49] reported that curcumin showed therapeutic effects against ulcerative colitis when colorectal cancer patients with liver metastases took 3.6 g/day of curcumin

orally for seven days, trace levels of curcumin metabolites were measured in liver tissue, but curcumin itself was not detected. In contrast, Garcea *et al.*, [49] observed that curcumin was measurable in normal and malignant colorectal tissue after patients with advanced colorectal cancer took 3.6 g/day of curcumin orally for seven days.

Muthu *et al.*, [50] study concluded that curcumin administration resulted in an increase in body weight, number of apoptotic cells, and p53 expression, while it decreased TNF-α level in serum. Curcumin treatment could improve the general health of colorectal cancer patients, probably, but not necessarily, due to the increase in p53 expression.

Reports of NIHC, [51] stated that the level of prostate-specific antigen (PSA) was decreased in most patients and was normalized in 36% of them, and the co-administration of curcumin with drugs showed no toxicity further than adverse effects already related to docetaxel monotherapy. Many registered phase I/II clinical trials designed to investigate the effectiveness of curcumin alone or with first-line treatment in patients with breast, prostate, pancreatic, lung, or colorectal cancer are under way.

To date, most of the controlled clinical trials of curcumin supplementation in cancer patients have been phase I trials, which are aimed at determining feasibility, tolerability, safety, and providing early evidence of efficacy. Preliminary evidence suggest curcumin may be protective against the development and progression of colorectal cancer through several mechanisms such as antioxidant activity, immunomodulation, promoting programmed cell death, antiproliferative effects, and epigenetic modification of cancer cells. This review gives suggestion to highlights eats curcumin daily to promote a healthy anti-cancer intestinal environment and fight colorectal cancer naturally.

Conclusions

The necessitate for alternative and less toxic therapies for colon cancer is apparent. As a natural product, curcumin is both non-toxic as well as diversified in its inhibitory effects on a multitude of pathways involved in carcinogenesis and tumor formation. Curcumin's lack of systemic toxicity and broad-reaching mechanism of action may make it best suited as an adjuvant therapy for colon cancers that are resistant to currently available therapies. However, curcumin has established itself as a safe and promising molecule for the prevention and therapy of not only cancer but also other inflammation-driven diseases without any side effects. This review gives suggestion treatment of colon cancer by dietary supplement curcumin. Finally a clinical application of curcumin is useful for future research.

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