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Review on Curcumin Bioactivity as a Potent Therapeutic Prospect for the Treatment of Cancer

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Abstract

Cancer is a leading cause of mortality that is characterized by uncontrolled cell proliferation above hay-flick limit (tumor growth), hypoxia in affected tissue and resulting to angiogenesis, apoptosis and metastasis. It adversely affects patients: psychologically, socially as well as economically. It results due to interplay of risk factors like; chemicals, viruses, genetic predisposition and environmental factors. There is global quest for safer, effective and cheaper strategies in cancer treatment which include use of phytochemicals obtained from plants. Turmeric has a very potent component, curcumin that has greatly contributed towards the effective treatment of cancer. Curcumin possesses some properties that inhibit cell proliferation and simultaneously induce apoptosis as well as provide positive results in management of oxidative stress and inflammation. It has been reported in animal cell line and clinical trial to be highly effective in cancer treatment due to its availability, bioactivity and no observable adverse effect. The use of curcumin in cancer treatment needs to be encouraged by promoting its use in preparation of regular cuisines and as adjuvants in cancer treatment.

Keywords: Adjuvants, Cancer, Curcumin, Metastasis, Phytochemicals

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INTRODUCTION

Cancer is characterized by abnormal growth of cells which proliferate uncontrollably and metastasize (Yadav & Mohite, 2020). This disease condition is as a result of successive genetic and epigenetic altercations resulting in cells evading apoptosis, uncontrolled cell proliferation, metastasis and angiogenesis (Carbone, 2020). According to cancer statistics (2023), cancer is a major public health concern globally and it ranks as the second leading cause of death in the United States.

Plant herbs are staple in every home and can be used as spices, herbal supplements, skincare and for medicinal purposes. A prime example is the plant Turmeric (*Curcuma longa*). The major phytochemical present in tumeric is curcumin, responsible for its bright yellow/orange color (Abd El-Hack *et al*., 2021). Curcumin is widely reported for its anti-tumor activity due to its ability to inhibit cell proliferation and simultaneously induce apoptosis. Its role in management of oxidative stress and inflammation also account for the above effect (Abu-Hijleh, *et al*., 2024). Currently, some cancer therapies even though described as effective have some limitations and side effects (Patel *et al*., 2021). The aim of this paper is to provide an insight to curcumin as a positive agent in the treatment and cure of cancer. It highlights medicinal potential of curcumin as an anti-cancer agent. Thus, the focus herein will be on its anti-cancer phytochemical properties.

Pathophysiology of cancer

Cancer is associated with the abnormal growth of cells above hay-flick limit. This growth results from accumulation of cells, commonly known as a tumor (Anderson *et al*., 2020). These cells become malignant when they evade cell signalling feedbacks like contact inhibition and anchorage dependence. Once a cell becomes malignant, it metastatized, which involves differentiation of cells at primary site and afterwards, travel through blood vessel to invade secondary sites. (Anderson *et al*., 2020). This arises majorly due to gene mutation. Oncogenes and tumor suppresor genes are mutated versions of protocogenes that are responsible for the growth factors and receptors, thus ensuring normal cell survival and proliferation (division) resulting in cancer development (Williams *et al*., 2022). The activation of oncogenes leads to cancer development.

Tumor grading and cancer staging

The United State National Cancer Institute explains that tumor grade describes the degree of abnormality observed when cancer cells are studied using microscope. The degree of cell abnormality is directly proportional to the aggressiveness of the more abnormal. The more aggressive the cancer is, the faster it grows and spreads. The institute states that cancer stage refers to the tumor size and the extent to which it has metastasized. Comparison of cancer cells with normal cells after biopsy has been used in grading and stagging cancer cells. The four main stages include: stage 1 (Cancerous cells are localized in a small area), Stage 2 (there is increase in size of cancerous cells) stage 3 (increased colony cells and spread to other parts of the body), stage 4 (most lethal stage where cancer cells as increased and spread to most parts of the body) (National Cancer Institute, 2023).

Evolution of cancer therapy

In this age, most utilized medical techniques in the treatment of cancer include surgical excision, chemotherapy, radiotherapy and immunotherapy (Verma *et al*., 2021). The field of Precision medicine, in recent past years, has focused on biomarkers in place of the conventional anatomic site of origin for given tumor cancer treatment (Gambardella *et al*., 2020).

Beginning of the 20th century is regarded for the advancements in cancer surgery techniques. This evolution in conventional radiotherapy and chemotherapy has seen radical surgeries gradually replaced less extensive surgeries (Verma *et al*., 2021). The National Cancer Institute defines radical surgery as that done to remove tumor and the surrounding tissues to which it may have metastasized to, as well as lymphatic drainage to ensure complete cure.

Unlike the first radical hysterectomy performed in the year 1906 by Wertheim, modern surgeries involve non-invasive procedures. At the moment, the current most promising therapy which has shown positive results in clinical trials is immunotherapy. This modality of cancer therapy activates or sensitizes the immune system to kill the cancer cells. Monoclonal antibodies recognize specific molecules on surface of cancer cells. It works by binding the antibody to the targeted molecule, which destroys the cells that express the said targeted molecule. Targeted therapies are less toxic than conventional chemotherapy because cancer cells are more dependent on target than the normal cells (Verma *et al.,* 2021).
In 2018, Nobel Prize was awarded to James Allison and Tasuku Honjo, for successful developing inhibitors of cell cycle checkpoints used in targeted therapeutic agents as seen in Precision medicine. The side effects of immunotherapy, organ inflammation, pain, swelling, soreness, nausea, high/low blood pressure, fatigue, et cetera, have been successfully reduced by the combination of nanomedicine with standard drug delivery systems to get better results (Verma *et al*., 2021).

The integrative approach to cancer treatment aims to treat not only the disease but to provide holistic treatment to the patient. This adjunct approach addresses factors which can help the patient deal with the symptoms of cancer and its clinical treatment (O'Brien *et al.,* 2020).

There are numerous curcumin nanoformulations which have been developed till date, the majority of which have focused on improving it solubility and bioavailability, as well as protecting it against hydrolysis which can render the molecules inactive. Other nanoformulations have focused on prolonged retention and circulation in the body, whereas the rest of them concentrated on intracellular release mechanisms and cellular delivery (Kabir *et al*., 2021). Curcumin can modulate the growth of tumour cells through several cell signalling pathways, including cell proliferation, cell survival, tumour suppressor death receptor, protein kinase and mitochondrial pathways (O'Brien *et al*., 2022). Figure 1 below shows its effect on various types of cancers.

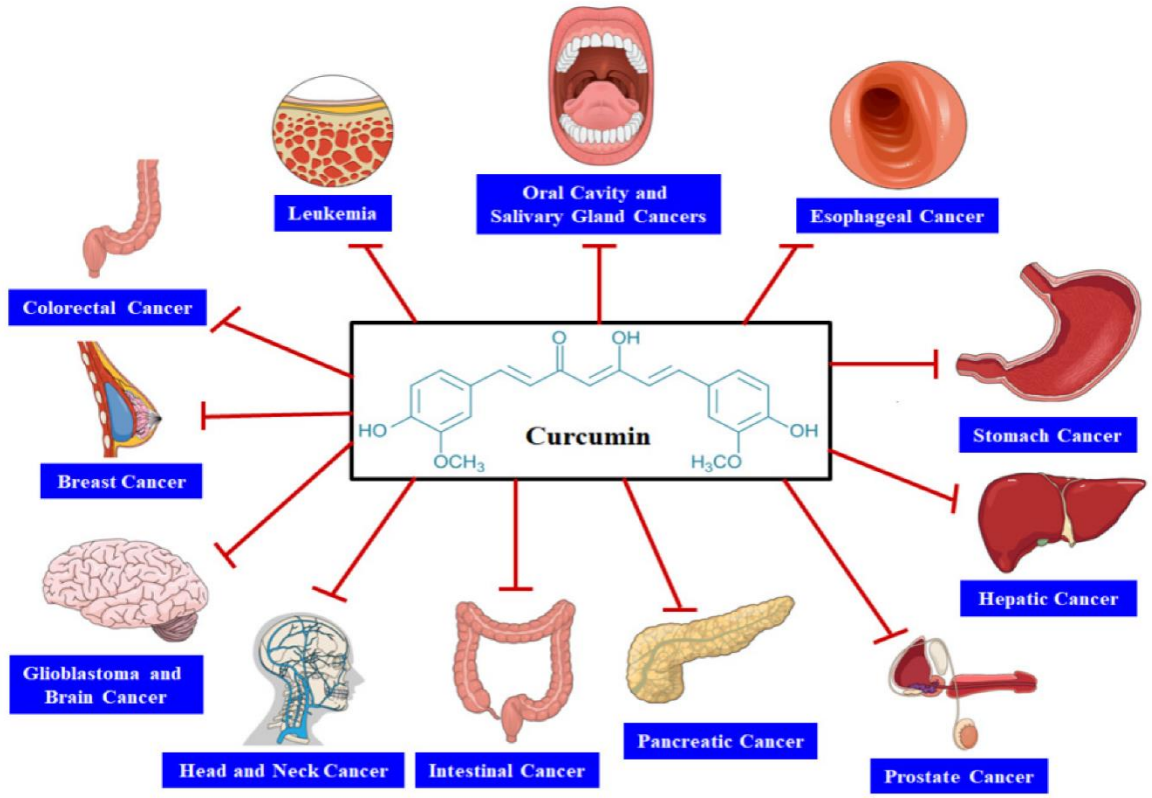

Figure 1: Curcumin plays a significant role in the treatment of multiple types of cancers (Tandir *et al.*, 2021).

Historical use of curcumin

Turmeric (*Curcuma longa*) –a rhizomatous herbal plant is said to have been used, in Vedic culture of India, as a culinary spice and believed to possess religious significance. Its active components are called curcuminoids; Curcumin, Demethoxycurcumin (DMC), Bisdemethoxycurcumin (BDMC). These curcuminoids can be isolated from the rhizome by specific processing to yield the active substances. A curcuminoid that has been of interest to researchers is Curcumin which supplies the Turmeric's yellow/orange coloration (Surbhi *et al*., 2020; Sonali *et al*., 2021).

The history of curcumin use is found to date back five thousand years (5000) ago. It is native to India but can be found in southwestern Asia. It was used characteristically as a home remedy for various diseases in Ayuvedic and Eastern medicine. Its use, therapeutically, reached the Western world during the age wherein the Portuguese ruled certain Indian states – in the 16th century (Surbhi *et al*., 2020).

According to Surbhi *et al.* (2020), various civilizations seemed to understand the medicinal and other useful properties of curcumin. Till date, the Japanese serve it in tea, the Thai use it in cosmetics, the Malaysians use it as an antiseptic, the Chinese use it as a colorant, the Pakistani use it as an anti-inflammatory agent, the Americans use it in various processed foods as a preservative and it is generally an essential ingredient in curries. The use of curcumin is approved by the United States Food and Drugs Administration as "Generally Recognized As Safe" (USA Foods and Drugs Administration, 2022).

Phytochemical properties of curcumin

The phytochemical properties of curcumin include its actions as: anti-viral, anti-inflammatory, anti-oxidant, anti-cancer, anti-bacterial, anti-allergy, anti-fungal, anti-arthritis, anti-venom, anti-diabetic, anti-obesity, pro-hemostasis, cardio and liver toxicity protection (Surbhi *et al*., 2020; Vadukoot *et al*., 2022).

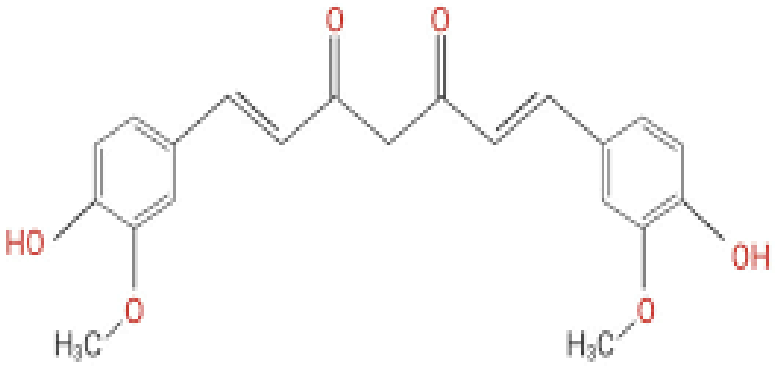

Figure 2: Molecular structure of Curcumin (Abd.Wahab *et al.,* 2020)

Curcumin (IUPAC nomenclature: 1, 7-bis (4-hydroxy-3methoxyphenyl)-1, 6-heptadiene-3, 5-Dione) is also called diferuloylmethane. It is a tautomeric compound; in organic solvents, it takes on enolic form while in water, it exists as a keto. The chemical formula of curcumin is $C_{21}H_{20}O_6$ with molecular mass 368.385 g/mol. Curcumin is the most abundant curcuminoid at 60% to 70% and contains three chemical entities: two oxy-substituted aryl moieties containing phenolic OH– groups, connected through a seven carbon chain consisting of a α, β unsaturated β-diketone moiety. The molecules of curcumin are hydrophobic and can undergo dehydrogenation by donation of hydrogen atoms in reactions, causing curcumin's oxidation. Some other reactions important for the biological reactions involving curcumin include hydrolysis, enzymatic reactions, degradation reactions and reversible/irreversible nucleophilic reactions (Mansouri *et al*., 2020; Surbhi *et al*., 2020; Yang *et al*., 2022).

Drug delivery of curcumin

Drug delivery as defined by Tiwari *et al.* (2012) is the method or process of administering a pharmaceutical compound to achieve a therapeutic effect in humans or animals. The delivery of curcumin as a drug is influenced by its solubility, mode of extraction, bioavailability, artificial synthesis and side effects and toxicity.

Solubility of curcumin

Research has found curcumin to be lipophilic. Thus, it is insoluble in water (hydrophobic) and ether but it is soluble in organic solvents such as ethanol and dimethylsulfoxide. It is the functional groups responsible for its solubility. It has also been found to be stable at pH of 1.5 to 3.5 which is the normal pH of the stomach. (Surbhi *et al*., 2020). "Interestingly, the anticancer activity of cucurmin has been limited primarily due to its poor water solubility, which can lead to low chemical stability, low oral bioavailability, and low cellular uptake." (Sonali *et al*., 2021; Tanvir *et al*., 2021).

Extraction of curcumin

The hydrophobic nature of curcumin makes use of organic solvents ideal for its extraction. After harvesting *C. longa*, the rhizomes- which are finger-like can measure 2cm to 8 cm in length and 1cm to 2cm in width, are boiled, dried and grounded to yield turmeric powder. This turmeric powder is then further processed to isolate curcumin. Widely referenced processing procedure is detailed involve ground turmeric is magnetically stirred in dichloromethane and heated (100 ℃) at reflux for an hour, the resultant mixture is filtered using a suction pump and the filtrate concentrated in hot water at 50℃, reddish-yellow residue is obtained and titrated with hexane. Thereafter, solid yield (curcumin) is collected by suction filtration. (Surbhi *et al*., 2020).

Bioavailability of curcumin

Surbhi *et al*. (2020) reported that the hydrophobic nature of curcumin was responsible for its accumulation in the hydrophobic regions, such as cell membranes thus, they can suppress oxidative stress by scavenging for reactive oxygen species and stimulates the action of superoxide dismutase. In fact, it has been demonstrated to be better than Vitamin E in control of oxidative stress. Due to low solubility in normal physiological media coupled with poor availability, a challenge being faced in the administration of curcumin is the achievement of optimum therapeutic concentrations.

Studies suggest that curcumin is first biotransformed to dihydrocurcumin and tetrahydrocurcumin, and subsequently converted to monoglucuronide conjugates. Preliminarily animal studies demonstrated that curcumin is rapidly metabolized and conjugated in the liver, and then excreted in faeces with limited systemic bioavailability. A 40 mg/kg body weight (b.w) intravenous dose of curcumin given to rats resulted in complete plasma clearance at one hour post-dose. An oral dose of 500 mg/kg b.w given to rats resulted in a peak plasma concentration of only 1.8 mg/Ml (He *et al*., 2011; Tiwari *et al*., 2021).

To increase the bioavailability of curcumin, it is administered with substances which block its metabolic pathways. One of such substances is piperine which is found in ~~b~~lack pepper and long pepper. Piperine has been proven scientifically to be an inhibitor of hepatic and intestinal glucoronidation. A research case study showed that with the administration of high curcumin dosage at 2000 mg/kg b.w and co-administration of piperine, systemic bioavailability was increased by 154% (Shoba *et al*., 1998; Choi *et al*., 2019).

Artificial synthesis of curcumin

The availability of curcumin as a nanomedicine is a wide field of research and several synthetic analogs of curcumin have been generated for potential therapeutic uses (Kabir *et al*., 2021; Pricci *et al*., 2020). The various effects of curcumin have been confirmed by numerous studies- both in *vivo* and *in vitro*, as well as by clinical trials. A hindrance to its common application clinically is its poor bioavailability which is as a result of the molecules being hydrophobic, thus, dissolving poorly in water. Solubility can be increased by combination of curcumin with nanoparticles such as polysaccharide and silica. Nanoparticles include particulate substances with dimension of at most 100 nm which has been applied in medicine and pharmacy to improve drug delivery (Gornicka *et al*., 2023).

Side Effects and Toxicity of Curcumin

Side effects seen in excess ingestion of curcumin have been reported to include nausea, diarrhea, headache, skin rash and yellow stool (Cheng *et a*l., 2001). Additionally, it is stipulated that addition of piperine (black pepper) extract may cause adverse drug reactions

due to the increased intestinal permeability caused by the combination. The majority of studies analyzing curcumin in cancer showed potentially beneficial effects and also additive or even synergistic effects on the efficacy of classical anti-cancer drugs (Willenbacher *et al*., 2019; Saghatelyan., 2020).

Experimental and clinical results of curcumin effects on apoptosis, metastasis, angiogenesis and inflammation in cancer

A major factor of cancer is the imbalance between cell death and cell proliferation. Programmed cell death, apoptosis is essential to maintain this balance. In the pathways involved in generation of apoptotic signals, the intrinsic pathway induces mitochondrial membrane to suppress the expression of B-cell lymphoma-extra-large (Bcl-xl) and B-cell lymphoma 2 (Bcl-2). Here, curcumin has been found capable of disrupting mitochondrial membrane potential balance, thus resulting in increased suppression of Bcl-xl. The extrinsic pathway, on the other hand, induces tumor necrosis factor-associated apoptosis and elevates death receptors on tissue cells with curcumin upregulating the expression of death receptors on cells (Tandir *et al*., 2021).

Studies conducted *in-vitro* proved that curcumin can stimulate apoptosis in cell lines by suppressing intracellular transcription factors which include; matrix metalloproteinase-9 (MMP-9), signal transducer and activator of transcription 3 (STAT3), cyclooxygenase II (COX-2), activator protein 1 (AP-1), nuclear factor-kappa B (NF-κB), and nitric oxide synthase (Tandir *et al.,* 2021).

Furthermore, curcumin's action as anticancer can be carried out via reduction in lactate production and reduction in glucose uptake by cancer cells through the downregulation of pyruvate kinase M2 enzyme. The suppression of this enzyme is by inhibition of rapamycin-hypoxia-inducible factor. In a nutshell, by interaction with various molecular targets, curcumin and its derivatives in nanomedicine can inhibit several cancer (Carvalho *et al*., 2020; Tandir *et al*., 2021).

Curcumin has been reported to increase patient survival time while simultaneously decreasing tumor markers' level (Mansouri *et al*., 2020). According to comprehensive reviews, curcumin achieves this aim by reducing the adverse effects of conventional cancer therapies, the anti-inflammatory effects of curcumin translate to its action as anti-tumor, as a result of the dependence of cancer on inflammation. Curcumin prevents the formation and growth of tumors by inhibiting Phase I enzyme which are involved in the production of toxic metabolites and carcinogens. On the other hand, curcumin activates Phase II enzymes which are essential in detoxification. Additionally, as an anti-cancer, curcumin interferes with the cell cycle to reduce the expression of cyclin-dependent kinases (CDKs) which are crucial in the control of cell cycle progression. In fact, a satisfying evidence shows that curcumin inhibits phosphorylation of STAT 3 gene, which is responsible for signaling of carcinogenic pathways (Choi *et al*., 2019; Mansouri *et al*., 2020).

Angiogenesis is defined as the process through which a new blood vessel forms from pre-existing blood vessels and is controlled by the equilibrium between anti-angiogenic and angiogenic factors. The pathophysiology of cancer or tumor growth causes low oxygen level (hypoxia) at tumor site. However, oxygen is essential to cell growth and in order to access increased levels of oxygen. The proliferating tumor cells, cell cycle genes, metastatic and drug resistant genes influence angiogenic dependent genes. This regulation is done by the action of genes such as hypoxia-inducible factor (HIF-1), insulin-like growth factor 2 (IGF2)

and transforming growth factor a (TGF-a). Imbalance in anti-angiogenic and angiogenic factors sustains the metastasis of cancer (Mansouri *et al.,* 2020).

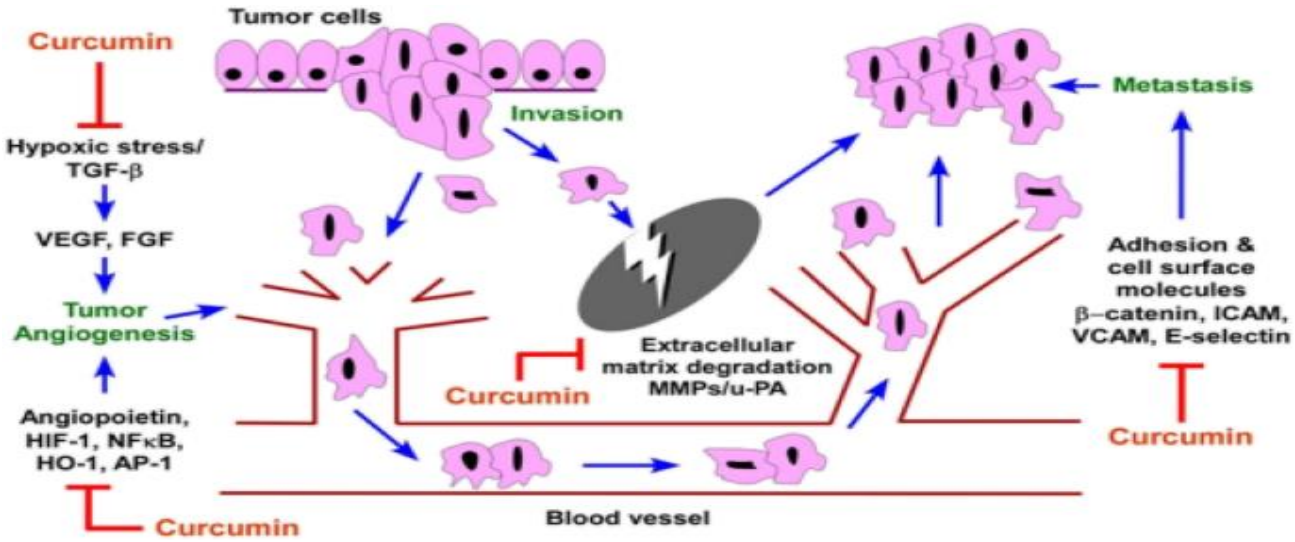

Figure 3; The effect of curcumin on angiogenesis and metastasis in cancer cells (Garg *et al.*, 2008).

In recent years, clinical trials have shown that administration of 300 mg/week of curcumin in combination to paclitaxel in 150 women after 12 weeks, resulted in reduction in fatigue, improved self-assessment of patients and response rate of metastatic breast cancer patients (Saghatelyan *et al.*, 2020). intake of 1.44 gram of curcumin for 6 to 36 months, resulted in suppression of prostrate specific antigen in 97 prostrate cancer patients (Choi *et al*., 2019). There was increased expression of P53 gene in 26 patients that were administered 1.08 gram of curcumin between 10 to 30 days in patients suffering from colorectal cancer (He *et al*., 2011).

Administration of 2, 4, 6, 8, or 12 g/day in 2 divided doses alone or with 10 mg/day of bioperine for 12 weeks in multiple myeloma (MM) patients showed suppression of NF-kB (p65), COX-2 and phospho-STAT3, this was more effective in mixed treatment with no associated toxic effect of curcumin (Vadhan-Raj *et al.,* 2007).

The use of curcumin as adjuvant has been very helpful in treating patients with cancer. This was reported by Zoi *et al*. (2021) when its combination with cholecalciferol in treatment of stage 0-II small lymphocytic lymphoma (SLL) or CLL was evaluated in a phase 2 clinical trial. This also increased overall survival rate.

Limitations to the use of curcumin in cancer therapy

In certain cases, curcumin showed no significant effect. An example is a randomized controlled trial wherein no significant efficacy was observed with nanocurcumin supplementation (120 mg/day) in prostate cancer patients treated with radiation. Another example is the trial where the administration of curcumin (6 g/d) for 6 weeks had no significant benefits in metastatic castration-resistant prostate cancer (Zoi *et al*., 2021).

In a study, oral curcumin was prescribed to the patients with adenomatous polyposis. This research was implemented to determine the safety and efficacy of curcumin in patients with adenomatous polyposis. In this study, 1500 mg of oral curcumin was administered twice per day over 12 months, to 44 patients with adenomatous polyposis. The results showed that

there was no significant difference between those who received oral curcumin and those receiving placebo (Hassanzadeh *et al*., 2020).

Oral intake of curcumin reduces bioavalability due to poor absorption in the intestine. However, biotransformation –chemical modification phases 1 and 2 in liver, is extensive and there is quick elimination via the gall bladder (Zoi *et al*., 2021). Nanoformulations of curcumin has increased bioavailability. However, they are not tissue specific in most cases since the drugs are delivered to both healthy and diseased body tissues (Ghoran *et al*., 2022).

CONCLUSION

Cancer therapy is not only expensive but harmful. The inclusion of curcumin obtained from dietary sources is cheaper and abundantly available. Curcumin can help solve or decrease the harmful effects of cancer therapy while augmenting the treatment process in cancer therapy as an affordable antioxidant. Curcumin, when included in diet can aid in the prevention of tumor generation. In addition, curcumin causes no significant side effects, even though its poor bioavailabity and fast metabolism remain major obstacles.

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