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Review Article

Role and Application of Curcumin as an Alternative Therapeutic Agent

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Abstract

The golden spice, turmeric has been an essential element in Asian culinary since many years. Curcumin is the major and important constituent of turmeric obtained from *Curcuma longa L*. Due to poor stability, solubility and biodegradability the effective concentration of curcumin was not able to reach to the tissues by oral consumption of turmeric in food. However, recent developments in drug delivery methods have elevated the formation of several nano-capsulation of curcumin. The formation of biodegradable nano-curcumin is one of the major breakthroughs for its therapeutic translation in humans and animals against various diseases. Since, ancient time it has been used for various ailments and also as a supportive therapeutic agent. Curcumin is now well-established therapeutic agent against cancer, neurodegenerative diseases, microbial infections, arthritis and other inflammatory disorders. It has hepatoprotective, immune-enhancer, cardiovascular and gastrointestinal effects. In this mini review article, we have explored the therapeutic role and application of curcumin in human diseases specifically as anti-bacterial and anti-cancer. The combinatorial study of curcumin with available drugs on different types of cancer has been discussed. We have also reviewed the types of nano-formulations available till date for curcumin and its role as therapeutic agent.

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Introduction

Curcuma longa L. also known as turmeric is a perennial herbaceous plant of the ginger family (*Zingiberaceae*). Turmeric plant reach about one meter in height and bear long leaves with petioles. The leaves emerge from the branching rhizomes that lie just below the soil surface. Older rhizomes are scaly and brown in color while young rhizomes are pale yellow to brown-orange. The small yellow-orange flowers are borne in the axil of waxy bracts that are pale green or tinged with purple [1]. Turmeric is traditionally used as a spice and coloring agent in food since many years and one of the most widely used spices throughout the world. However, later turmeric has been recognized for its medicinal importance. Turmeric is known by numerous names i.e. Yukon, Indian saffron, kurkum, yellow ginger, and kunyitbasah [2]. Studies have also strongly indicated that curcumin, the active compound in turmeric, is the key ingredient responsible for the major therapeutic activities of turmeric. Turmeric owes its yellow color to the curcumin, the main curcuminoid demethoxycurcumin (4-hydroxycinnamoyl-(feruloyl) methane), and bisdemethoxycurcumin (bis- (4-hydroxycinnamoyl) methane) all belongs to the diarylheptanoids. These pigments are obtained from the extraction of rhizome of turmeric [3]. Curcumin can be extracted from turmeric by different methods such as conventional extraction using Soxhlet, microwave-assisted extraction, ultrasound-assisted extraction and enzyme assisted extraction of curcumin [4].

Curcumin is a tautomeric compound exists in the enolic form in organic solvents and keto form in water. The molecular formula is $C_{21}H_{20}O_6$, molecular weight is 368.4 g/mol and melting point is 183℃. Curcumin has been used extensively in ayurvedic medicines as it is non-toxic to the greater extent and exhibits a variety of therapeutic properties, including antioxidant, analgesic, anti-inflammatory, and antiseptic. Curcumin or diferuloylmethane or 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadien-3,5-dione, is a polyphenolic natural compound and the major constituent of the rhizome of the turmeric. Previous studies showed that there is a difference in the curcumin content among different lines of *C. longa* species. Typically, turmeric contains approximately 77 percent diferuloylmethane (curcumin I), 17 percent desmethoxycurcumin (curcumin II), and 6 percent bisdemethoxycurcumin (curcumin III). Curcumin is an orange-yellow crystalline powder, practically insoluble in water and ether, but soluble in ethanol, dimethyl sulfoxide, and acetone. Biological properties exhibited by curcumin include anti-fungal, anti-inflammatory, anti-oxidant, anti-angiogenic, anti-HIV, neuroprotective, chemo-preventive, and anti-tumor [5].

Therapeutic Applications of Curcumin

Curcumin is considered as a pleotropic molecule because it possesses multiple beneficial effects on human body and preventive measurements against several diseases. Previous studies have

established curcumin as a potent antimicrobial, anticancer, anti -inflammatory and anti-oxidant molecule. Moreover, it also shows hepatoprotective, cardio protective and gastro protective effects.

Anti-Cancer Agent

Curcumin exerts anticancer effects in different biological pathways involved in mutagenesis, apoptosis, and metastasis. Curcumin helps in the elimination of reactive oxygen species, shows anti-inflammatory properties as a result of Cyclooxygenase enzyme (COX) inhibition and inhibits cell signal transduction through various mechanisms. These activities lead to observe an antineoplastic effect, which includes inhibition of tumor cell proliferation and suppression of chemically induced carcinogenesis. Cancer is one of the major public health menaces and the second leading cause of death in the world [6]. Although huge progress has been made in the field of cancer therapeutics but almost all the anti-cancer treatments available today have severe side effects on healthy cells and body. Therefore, it was hypothesized that we should include some supportive medicines with available drugs against cancer to nullify the adverse effect of anti-cancer therapy. Curcumin has multiple activities that are more effective for cancer treatment [6]. Curcumin has shown potential activity against many types of cancer either alone or in combination with other drugs. It is effective against colorectal cancer, pancreatic cancer, breast cancer, prostate cancer, multiple myeloma, lung cancer, oral cancer, Head and Neck Squamous Cell Carcinoma (HNSCC) [6]. The important mechanism by which curcumin has shown its anti-cancer activity is by inducing apoptosis and inhibiting proliferation and invasion of tumor by suppressing a variety of cellular signaling pathways. It is an inhibitor of the transcription factor NF-kB and downstream gene products (c-myc, Bcl-2, COX-2, NOS, Cyclin D1, TNF-α, interleukins and MMP-9) [7,8]. Curcumin has been shown to suppress cancerous cell growth [8].

Prostate cancer

Prostate cancer is the leading cause of death in men over 40 years of age. For the treatment of prostate cancer Docetaxel is clinically approved but it's prolonged use causes severe toxicity in patients. In a study, it was found that the combinatorial treatment of docetaxel (10nm) and curcumin (20μm) for 48h significantly inhibited the rapid cell growth and apoptosis in DU145 and PC3 cell lines of prostate cancer [8,9]. Curcumin enhances the efficacy of docetaxel on prostate cells by inhibiting growth and inducing apoptosis through modulation of tumor suppressor protein, transcription factor, and oncogenic protein kinase compared to docetaxel or curcumin alone [9].It has been shown that ursolic acid, curcumin, and resveratrol are also used in combination for the treatment of prostate cancer. These are the dietary phytochemicals which target inflammatory signaling pathways including Stat3 and NF-κB and hindered the cancer development and progression [10].

Breast cancer

Breast cancer has been identified as the most common type of cancer in the developing as well as developed countries. Mutation in BRCA1 and BRCA2 genes are the major cause of breast cancer. The frequency of BRCA1 mutation is 55-65% where as for the BRCA2 mutation is 45%. Doxorubicin is commonly used as a chemotherapeutic agent against breast cancer. It is an anthracycline antibiotic [11]. A combination of 45mg of DMSO (dimethyl sulfoxide) and Curcumin inhibited the development of intestinal adenomas and reduced the frequency of mutation in BRCA genes. This combination led to a drastic reduction in inflammation and apoptosis [12].

Colorectal cancer

This is the third most diagnosed type of cancer all over the world with high mortality. Bioactive dietary phytochemical compound resveratrol used with curcumin for great therapeutic potential. The combination can induce apoptosis in cancer cells. They have been shown to modulate several essential pro-apoptotic genes and signaling pathways related to colorectal carcinogenesis on two colorectal cell lines DLD-1 and CaCo-2. The study suggests that curcumin and Resveratrol are more effective in a dose-dependent manner for inhibiting the cell proliferation. In combination treatment IC_{50} value were 71.8 μm (20.5μm curcumin + 51.3μm Resveratrol) for DLD-1 cell lines and 66.21μm (18.9μm curcumin + 47.3μm Resveratrol) for CaCo-2 cell lines respectively [13].

Pancreatic cancer

Pancreatic Cancer (PaCa) is a major health problem due to its vicious behavior and early metastasis. It is the 5th most common cause of death in the United States [13]. Surgical resection is the only curative therapy for this disease. However, systemic gemcitabine-based chemotherapy and nab-paclitaxel are used for pancreatic cancer but it has many side effects and poor results. Several studies have demonstrated that curcumin has better pharmacological effects. A combination of nano-formulated curcumin with drug Gemcitabine has been used to control the tumor growth [14].

HNSCC (Head and Neck Squamous Cell Carcinoma)

It is the sixth most common cancer all over the world. Some anti-cancer drugs for the treatment of HNSCC (Head and Neck Squamous Cell Carcinoma) which have been used are Docetaxel, Doxorubicin (DOX), 5- Fluorouracil (5-FU) and Cisplatin (diamine dichloroplatinum (II), CDDP). However, they have a limitation due to their non-specificity, drug resistance, and toxicity in patients. A combinatorial approach with curcumin may increase the efficiency of these chemotherapeutic drugs and reduce toxicity. Curcumin exhibited significant effect on cell growth and enhanced apoptosis in NT8e cancer cell lines with a combination of 5-FU or DOX. This combination shows cell cycle growth arrest at the G1/S phase [15] (Table 1).

Anti-inflammatory

Arthritis is a more common problem of obese people world-wide which is characterized by joint inflammation. Several studies showed that curcumin serve as a potent pain reliever and decreases the onset of symptoms of inflammatory diseases compared to the harmful steroidal and nonsteroidal pain medication [19]. Documented the effectiveness of hydro- alcoholic extract of turmeric was incontestable to inhibit joint inflammation and periarticular tissue destruction during a dose-dependent manner. A recent study indicated that oral administration of curcumin was effective in attenuating the leukocyte inflammatory response against zymosan-induced inflammatory disease model in rats suggest that curcuminoid treatment represents a good and safe alternative therapy for arthritis. Arthritis patients respond very well to curcumin supplementation with balanced diet and exercise. It is evident that curcumin could be a potent alternative therapy for inflammatory diseases. it inhibits the biosynthesis of inflammatory prostaglandins and arachidonic acid [19].

Type of cancer	Combinatorial drug regime#	Outcome	References
HNSCC (Head and neck squamous cell carcinoma)	5-FU, doxorubicin, and cisplatin with curcumin	Exhibited significant growth inhibition and enhanced apoptosis in NT8e cancer cells.	[15]
Colon Cancer	5FU-TCS-NPs and CRC-TCS-NPs+curcumin 5-fluorouracil loaded thiolated chitosan nanoparticles(5FU-TCS-NPs). Curcumin loaded thiolated chitosan nanoparticles (CRC-TCS-NPs).	Enhanced anticancer effects on colon cancer cells in vitro and improved the bioavailability of the drug in vivo.	[16]
Neuroblastoma	Curcumin with doxorubicin.	Increased cell death in a panel of neuroblastoma cell in vitro, reduce tumor burden.	[17]
Metastatic Prostate Cancer	Docetaxel and Curcumin.	DU145 and PC3 cell lines of Prostate Cancer were treated.	[9]
Colorectal Cancer	Curcumin and Resveratrol	Modulate a plethora of signaling pathways.	[13]
Breast Cancer	Curcumin and doxorubicin.	Suppress EMT (Epithelial-to-mesenchymal transition), inhibit TGFβ and PI3K/kiAKT pathway, and proliferation.	[11]
Stomach Cancer	Curcumin with 5-FU or 5FU plus oxaliplatin (FOLFOX).	Reduces the progression of gastric cancer and inhibit MNNG-induced duodenal tumor.	[11]
Leukemia	Methotrexate (MTX) with curcumin.	Curcumin enhanced the cytotoxic activity of MTX.	[11]
Lung Cancer	Carboplatin, doxorubicin,gemcitabine, paclitaxel or curcumin and doxorubicin (Cur-DOX).	Reduce the expression of NF-κB, MMP-9, and COX and indirect apoptosis in H1299 and A549 cells.	[18]
Bladder Cancer	Cisplatin + curcumin.	Upregulate the expression of phospho-mitogen- activated protein kinase (p-MEK) and phospho- extracellular signal-regulated kinase 1/2(p- ERK1/2) signaling in bladder cancer cell lines. (253J-Bv and T24)	[18]
Liver Cancer	Curcumin and 5-FU or curcumin and doxorubicin.	Enhanced cytotoxicity and decrease inhibitor concentration in HepG2 cells.	[18]

Table 1: Combinatorial drug regime used for different types of cancer and their effect.

#Abbreviations of drug regime used in the table 1:

5- FU-TCS-NPs: 5-Flurouracil loaded Thiolated Chitosan Nanoparticles
CRC-TCS-NPs: Curcumin Loaded Thiolated Chitosan Nanoparticles
EMT: Epithelial-to- Mesenchymal Transition
TGFB: Transformin growth factor ß
AKT: serine/threonin specific protein kinase
FOLFOX: 5FU Plusoxaliplatin
MTX: methotrexate
MNNG: N- methyl-N' nitro-N-nitrosoguanidne
DOX: doxorubicin
COX- cyclooxygenase
NFkB- Nuclear factor-kappa ß
MMP-9: Phospho- matrix metalloproteinase-9
P- MEK: Phospho-mitogen- activated protein kinase
P-ERK: Phospho- extracellular signal regulated kinase

Inflammation is caused by illness, trauma or stress and helps the body to fight against foreign invaders. Although acute (short term) inflammation is helpful but once it is in chronic (long term) state, becomes harmful for its own tissue and organs. It has been established that chronic inflammation is the root cause of several disease such as arthritis, diabetes, heart diseases, metabolic syndromes, Alzheimer's and cancer. Therefore, it is necessary to prevent inflammation in its acute phase so that the onset of these diseases can be prevented. Recently, curcumin has been shown to be potent anti-inflammatory molecule and can suppress the molecular pathways of inflammatory response. Curcumin blocks NF-kB molecules that travel into the nuclei of the cells and activate genes associated with inflammation. NF-kB is believed to play a significant role in several chronic diseases [20].

Anti-thrombotic

Thrombosis mainly occurred by platelet activation and aggregation. Vascular obstruction causes serious disease such as angina, ischemic stroke, and heart attack. Recent increase in thrombotic diseases advocates alternative therapy that is necessary for the prevention and treatment of arterial thrombosis without adverse side effects [21,22]. Curcumin has antithrombotic effect on platelet functions. It has been used for the removal of obstruction in blood circulation and has beneficial effects in cardiovascular ailments. Curcumin is regarded as a safe alternative agent as the oral administration of curcumin (8g per day) did not show any side effects. Furthermore, in vitro studies have shown that curcumin has a significant inhibitory effect on Platelet Activation Factor (PAF) induced platelet aggregation, thus curcumin has a potential in the reduction of platelet activation and aggregation [21].

Antioxidant

Free radicals are extremely reactive molecules with mismatched electrons that tend to react with vital organic compounds like fatty acid, protein, or DNA. The oxidative damage could lead to the serious life-threatening diseases and cancer. Curcumin has a potent antioxidant property which works as a scavenger for free radicals and increase the capability of our immune system to fight against oxidative damage Curcumin conjointly boosts the activity of the inhibitor enzymes that work against the free radicals and blocks them directly. Curcuminoids present in turmeric are strong antioxidants as they function in three ways: 1) It makes the balance between the pro-oxidant and anti-oxidant species in the body; 2) It increases the level of anti-oxidant enzymes and 3) scavenge the free radicals' that causes oxidative damage. Curcumin inhibit the peroxidation of lipids, synthesis of

Lipoxygenase (LOX), arachidonic acid and Cyclooxygenase (COX) enzymes which are involved in steroidal hormone synthesis [22].

Anti-microbial activity

Curcumin has a potent antimicrobial activity. Curcumin inhibits the synthesis of protofilaments or increase sensitivity for ß-lactam antibiotics. It can increase the sensitivity of several antibiotics like cefixime, cefotaxime, vancomycin, and tetracycline. Previous studies suggest that use of curcumin with antibiotics increases the Zone Of Inhibition (ZOI). Combination of curcumin with cefotaxime increases the ZOI by (24.9%), with vancomycin (26.5%), and with tetracycline (24.4%) respectively against *S. aureus* [23].Curcumin is effective against both methicillin resistant *staphylococcus aureus* (MRSA) and methicillin sensitive *Staphylococcus aureus* (MSSA) [24]. Curcumin has capability to reverse the MRSA strain of *S. aureus* to MSSA strain by modulating the peptidoglycan in bacterial cell wall.

In developing countries, Acute Diarrheal Disease (ADD) is an important health problem. Some pathogen which is responsible for diarrhea are *E. coli, Salmonella typhi, Bacillus cereus, Campylobacter jejuni, Aeromonas hydrophita, Shigella* app, *Yersinia* spp.*, Vibrio cholera, Giardia intestinalis and Cryptosporidium parvum.* Enterotoxigenic *E. coli* (ETEC) is one of the most common causative agents which is responsible for diarrhea illness. ETEC is also resistant to Ampicillin, Amoxicillin/Clavulanic acid, and Cifazalin. However, the use of curcumin enhanced the antibacterial activity of most antibiotics. 330 µg/ml of curcumin with antibiotic increases the activity of Ceftazidime (74.2%), Amoxicillin/Clavulanic acid (56.2%) and Amoxicillin (56.2%) [25].

Hepatoprotective action

Curcumin exhibits the protective phenomenon against the liver damage. An in vivo study was done with carbon tetra chloride (CCl_4) on hepatotoxicity at a dose of 3ml/kg/day for 3 months. The study showed marked increase in transaminases, alkaline enzyme and plasma levels of γ-glutamyl transpeptidase thiobarbituric acid and lipoperoxides, and decrease in plasma levels of glutathione, vitamins C and E. However, the administration of curcumin with CCl_4 considerably reduced these phenomena within the plasma, kidneys, and liver. Additionally, the study also concluded that use of curcumin decreases the tissue damage in these organs. Curcumin also prevents CCl_4-induced liver damage by inhibiting the activation of NF-kB and hemoprotein P450 within the liver [20].

Nano-curcumin formulations and its role as therapeutics

Curcumin has significant therapeutic effects. However, its bioavailability is very poor because of poor absorption, rapid metabolism, and rapid systemic elimination [26]. To improve the biological activity and bioavailability of curcumin various techniques like micro and nanotechnology have been used.One of the major limitations of curcumin for its biological use are solubility and stability. Its solubility depends on the pH of the medium [27]. Nano-formulation of curcumin is the best way to improve its clinical therapeutic modality. Nano-formulation enhances its solubility and specificity for the tissue of interest and site-specific delivery of curcumin with high permeability and great performance [28]. Biodegradable polymer-based Nanoparticles (NPs) such as PLGA (Poly-L-Glycolic acid) has potency to use in human also because they can be easily degraded in CO_2 and H_2O and approved by FDA for use in human. Beside PLGA there are several other compounds which have been used for curcumin nanoformulation such as liposomes, micelles, nanogels, cyclodextrin, solid lipids, gold, silver etc. These nanoparticles have been studied in various disease models and shown to improve therapeutic outcome against many types of disease such as cancer, skin wounds, Alzheimer, epilepsy, inflammatory diseases, multiple sclerosis, Parkinson's disease [26,29].

Liposome contains phospholipid bilayer and spherical in shape. Phospholipid vesicles protect drugs from external stimuli and increase biosafety and biocompatibility [30]. It Enhances Permeation and Retention (EPR) effect which is very important in cancer therapeutics. Its size varies from 25nm to 2.6mm (26). Curcumin loaded liposome composed of Dimyristoyl Phosphatidylcholine (DMPC) and cholesterol resulted in 70-80% suppression of prostate cancer in cell line CNCaP and C4B2 study [30].Several types of nano-formulation have been made for curcumin and studied for various types of cancers (Table 2).

Discussion

We have summarized the role of curcumin in human diseases specifically in cancer as an alternative therapeutic agent in this review article. Curcumin has been shown to be a potent anti-cancer, anti-bacterial agent but few drawbacks of curcumin hinders its vast use as a therapeutic drug. The major drawbacks of curcumin are poor solubility in water since it is a phenolic compound, its poor stability and biodegradability within the living organism. Therefore, nanoformulation of curcumin is gaining more importance than using it alone. We have discussed the various compounds used for the formation of nanoparticles used against different types of human cancer. Since, anti-cancer drugs available today possess toxicity on noncancerous cells and effect the patient's life in many ways, it is hypothesized that we should include some natural compounds with the available drugs so that the toxic effects of these drugs can be suppressed. The other way to control the toxic effects of chemotherapeutic drugs by passive and active targeting of drug. In passive targeting chemotherapeutic drugs such as Doxorubicin (DOX) [31] and curcumin [32] are encapsulated in PLGA nanoparticles that protect the drugs form the interaction with the fluids present in the body thus increases the circulation time of the drug. It also protects the drugs from early degradation and increases the stability. The active targeting represents the attachment of ligands or specific antibodies on the surface of nanoparticles. For example, attachment of antibodies against protein A (Spa) of *S. aureus* on the gold nanoparticles specifically target the *S. aureus* cells at the infection site [33]. Recently many herbal compounds extracted from plants and herbs have been used in combinatorial drug therapy against human disease such as Neem, babul, black pepper, turmeric and many more. Curcumin is a major component of turmeric or *Curcuma longa L.* and has been shown to possess significant anti-cancer and ant-bacterial properties however; curcumin alone can't solve the whole problem. Therefore, combinatorial drug therapy is the better way to treat these diseases. Researchers have shown that combination of curcumin with available drugs have shown better outcome than curcumin or drug alone (Table 1). As PLGA is the only compound which is approved by FDA for the use in humans, we hypothesized that curcumin as PLGA-cur-nanoparticles can also be used in animal models and humans against various diseases.

Types of nanoparticles	Therapeutic application	Function	Reference
Liposome	Prostate cancer Pancreatic cancer Breast cancer	High bioavailability	[26,30]
Micelle	Lung cancer Breast cancer	Protect curcumin from degradation, improve stability, enhance its circulating time and target specificity	[26,29,11]
Nanogel	Pancreatic cancer Breast cancer	Enhance fluorescence effect, hydrophilicity	[26,29]
Chitosan	Melanoma cancer HNSCC Colon cancer	Improved drug delivery system	[26,29,11]
Dendrimer	Colon cancer Breast cancer	Improve anti-tumor properties	[26,16]
Noisome	Pancreatic cancer	Hydrophilic, amphiphilic, lipophilic moieties, behave similarly to liposome	[26]
Cyclodextrin	Breast cancer Lung cancer Pancreatic cancer Prostate cancer HNSCC Wound healing	Hypocholesterolemic properties	[26,14]
Gold	Anti-cancerous	Enhance solubility, increase cytotoxicity prolongs the blood circulation	[26,29]
Solid lipid polymer	Breast cancer	Increase photostability, of curcumin, protect from pH mediated degradation	[26,29]

Table 2: Various types of nanoformulation and its use against human cancer.

These nanoparticles can be combined with available drugs and can be used for biofilm associated infections, indwelling implant infections caused by bacteria and even cancer. However, further systemic research is needed to prove the efficacy of combinatorial drug therapy in animal models and their dosage response.

Conflict of Interest

On behalf of all the authors, the corresponding author states that there is no conflict of interest for this article.

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