

CURCUMIN - NATURE'S PRECIOUS MEDICINE

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Abstract: Herbal medicine is dated into prehistoric time and has many advantages over the modern medicine. Reason for success of herbal medicine is due to lowered side effects and Curcumin Longa, i.e., turmeric, a herb, has its uses dated in vedic texts and other religious texts also. Curcumin has a very large therapeutic window covering many types of ailments. It has excellent safety profile and has a very narrow window of adverse complications. In our review we present the various pharmacological indications and therapeutic applications of curcumin viz., anti-microbial, anti-inflammation, anti-diabetic, anti-fungal, anti-oxidant, anti-cancer, etc. This review provides a brief overview of the potential health benefits of curcumin.

Keywords: *Curcumin longa, Ancient Indian medicine, Herbal and Traditional medicine, Anti-inflammatory, Anti-oxidant.*

INTRODUCTION

Turmeric is an Indian rhizomatous herbal plant curcuma longa of the ginger family zingiberaceae of well-known medical benefits the medicinal benefits of turmeric could be attributed to the presence of active principles called Curcuminoids. Desmethoxy curcumin [DMC] and Bisdemethoxy curcumin [BDMC] are collectively known as curcuminoid[1]. Curcumin a bright yellow spice derived from the rhizome of Curcuma longa Lin was primarily isolated by Vogel[1842] and was characterized by Milobedeska and colleagues[1910] it was synthesized and confirmed in 1913 by Lampe and colleagues' natural product-based remedies are popular in health management and its importance in health cure documented in religious literatures[2].

Turmeric is a plant known by its medicinal use, dating back to 4000 years ago in the vedic culture in India, where it was used as culinary spice and had some religious significance it has been used traditional as a medicinal herb due to its various advantages such as antioxidant, anti-inflammatory, anti-mutagenic, antimicrobial, and also in herbal and traditional medicine treats rheumatoid arthritis, chronic anterior eye inflammation, conjunctivitis, skin cancer, small pox, wound healing, urinary tract infections and liver ailments, strengthening the overall energy of the body, dispelling worms, regulating menstruation, dissolving gallstones, cleansing wound and even for various digestive disorders[3,4]. In the ancient Indian medicine of Ayurveda, turmeric paste, a topical agent, has been used to treat common ocular infections and inflammations.

Powdered turmeric has been consumed with hot milk for cure of cough and related respiratory problems. Roasted turmeric is administered as an anti-dysenteric agent. This ancient medicine was also used for treatment of other digestive disorders such as indigestion, dyspepsia, flatulence, gastric and duodenal ulcers[5].

Curcumin, 1,7-bis(4-hydroxy-3-methoxy phenyl)-1,6-heptadien-3,5-dione, is a lipophilic molecule that rapidly permeates cell membrane. It affects the function and structure of the cell membrane and mimics typical events happening during the apoptosis process, as it induces immediate and partly reversible loss of membrane integrity, where cell could recover in a relatively short time[6].

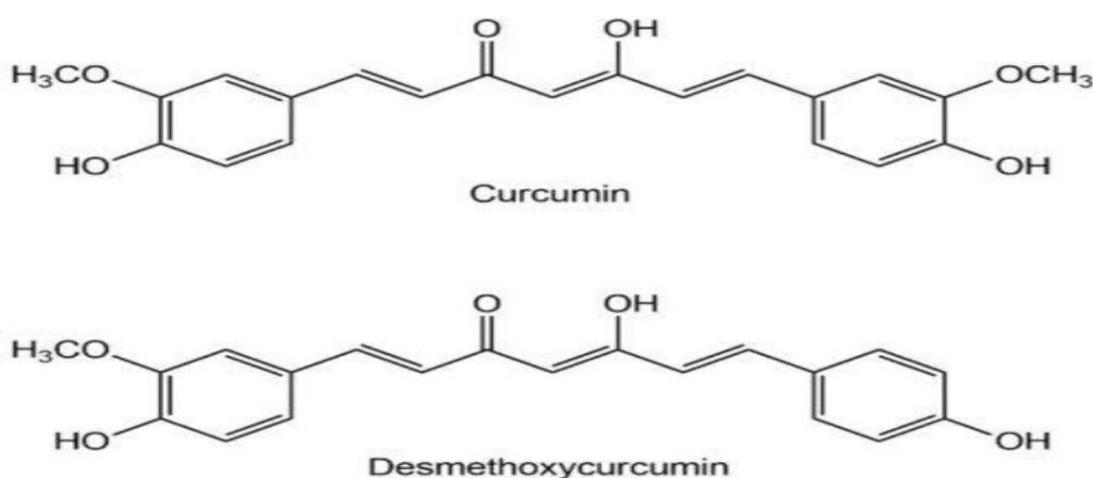


Figure 1: Curcumin, Desmethoxy curcumin.

Curcumin is available in several forms including capsules, tablets and ointments and was approved by USFDA as "Generally Recognized as Safe" (GRAS)[7]. Curcumin is remarkably well tolerated, but its bioavailability is poor and does not appear to be toxic to animals or humans [8].

The National Toxicology Program [NTP], evaluated the short-term toxicity as well as long-term toxicity of curcumin with different concentrations [doses of 50 to 2600 mg/kg] for a period of 13 weeks or 2years in rats and mice. Curcumin can perform as a hydrophobic reducing [antioxidant] agent and there by scavenging various free radicals and also demonstrates as a better suppressing oxidative agent than vitamin E.
MECHANISM OF ACTION

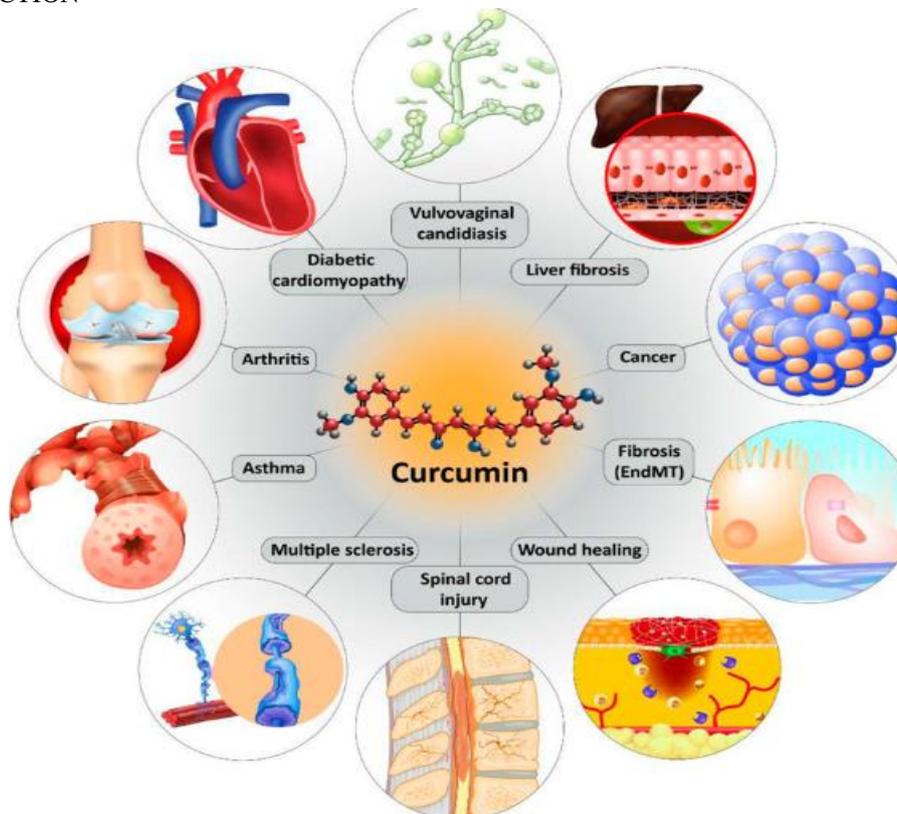


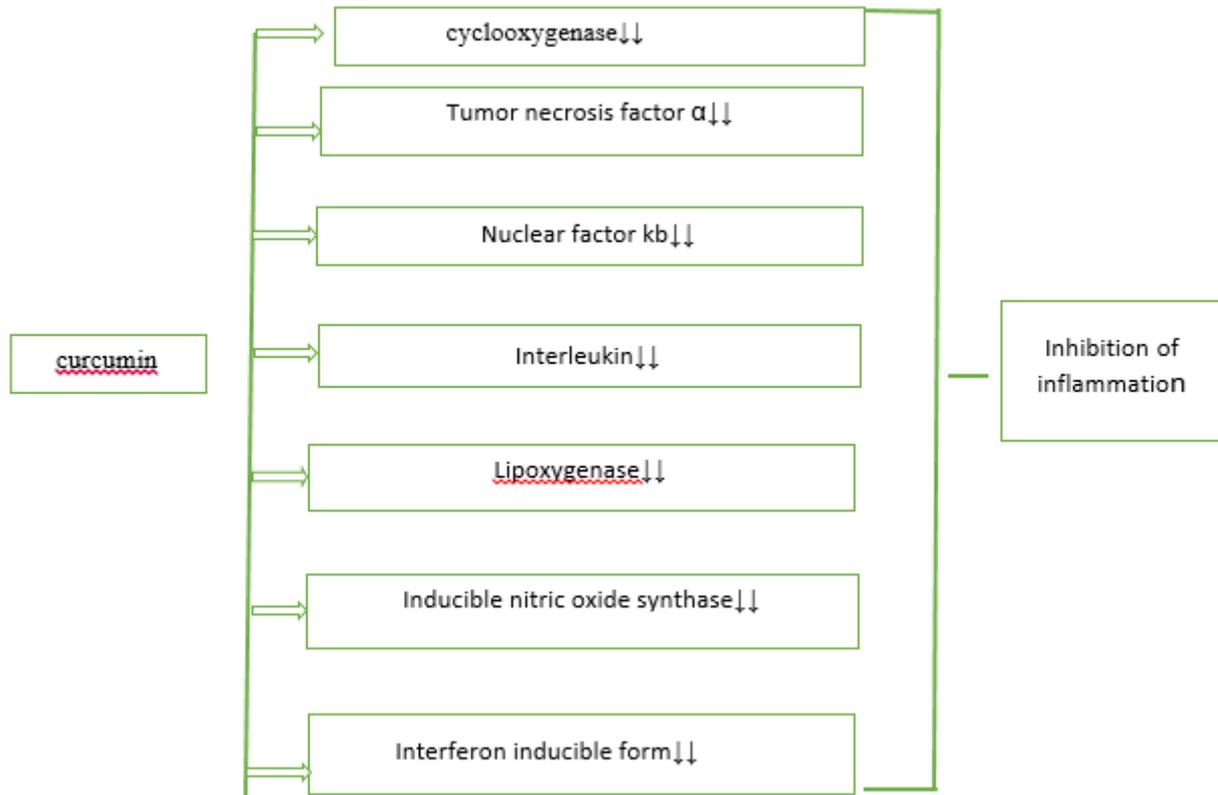
Figure 2: Mechanism of action of curcumin in different organs.

ANTI INFLAMMATORY

For thousands of years curcumin has been known to possess anti-inflammatory ability. Many of the activities associated with curcumin are related to its ability to suppress acute and chronic inflammation[9]. Curcumin regulates numerous transcription factors, cytokines, protein kinases, adhesion molecules, redox status and enzymes that have been linked to inflammation[10].

Tumor Necrosis Factor ($\text{TNF-}\alpha$) is a major mediator of inflammation in most diseases, and this effect is regulated by the activation of a transcription factor, nuclear factor(NF-KB). Nuclear factor kappa-B (NF-KB) plays a critical role in signal transduction pathways that are involved in inflammatory diseases and various cancers[11]. The (NF-KB) protein resides in cellular cytoplasm inactively, but following their activation, which requires activation of various kinases and phosphorylation and degradation of activation inhibitors such as IKB, that are translocated to the nucleus; curcumin was shown to inhibit TNF- dependent (NF-KB) activation, as well as other activation pathways induced by various agents in which reactive oxygen, an intermediate was produced.

COX-2, the inducible form of cyclooxygenase, predominates at inflammatory sites, and also plays a critical role in tumor promotion[12,13]. Curcumin decreases the expression of COX-2 enzyme and inhibits the expression of pro-inflammatory enzyme 5-LOX; it also reduces of various inflammatory cytokines such as TNF, IL-1, IL-6, IL-8, interferon γ and some other chemokines[14]. Curcumin, a chief ingredient of turmeric inhibits arachidonic acid metabolism and inflammation in epidermis by regulates cyclooxygenase and lipoxygenase pathways.



Curcumin as anti-inflammatory in inhibition of various genetic pathways

ANTI-MICROBIAL ACTIVITY

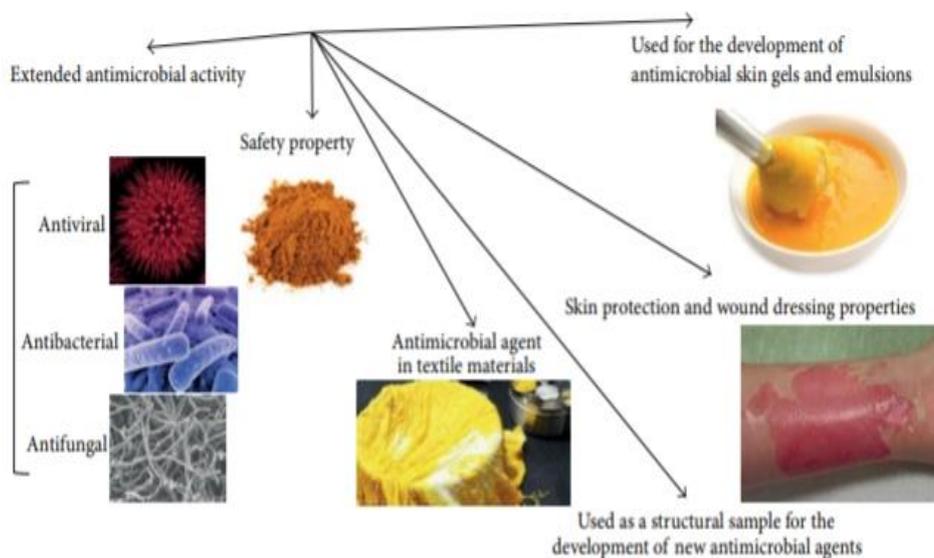


Figure 3: Importance of curcumin in antimicrobial studies.

Drug resistance for microorganisms is rapidly growing worldwide, a safe and effective natural source is needed to overcome such types of problem. Curcumin, was observed to have anti-bacterial, anti-viral anti-fungal activities[15]. A study finding revealed that curcumin exhibited inhibitory activity on methicillin-resistant staphylococcus aureus strains with minimum inhibitory concentration value of 125-250ug/ml[16].

Curcumin, also inhibits the growth of all Helicobacter pylori stains *in vitro* that were isolated from infected patients suffering from gastrointestinal disorders. Curcumin possess anti-bacterial property against a number of Gram-positive and Gram-negative bacteria[17].

ANTI-FUNGAL ACTIVITY

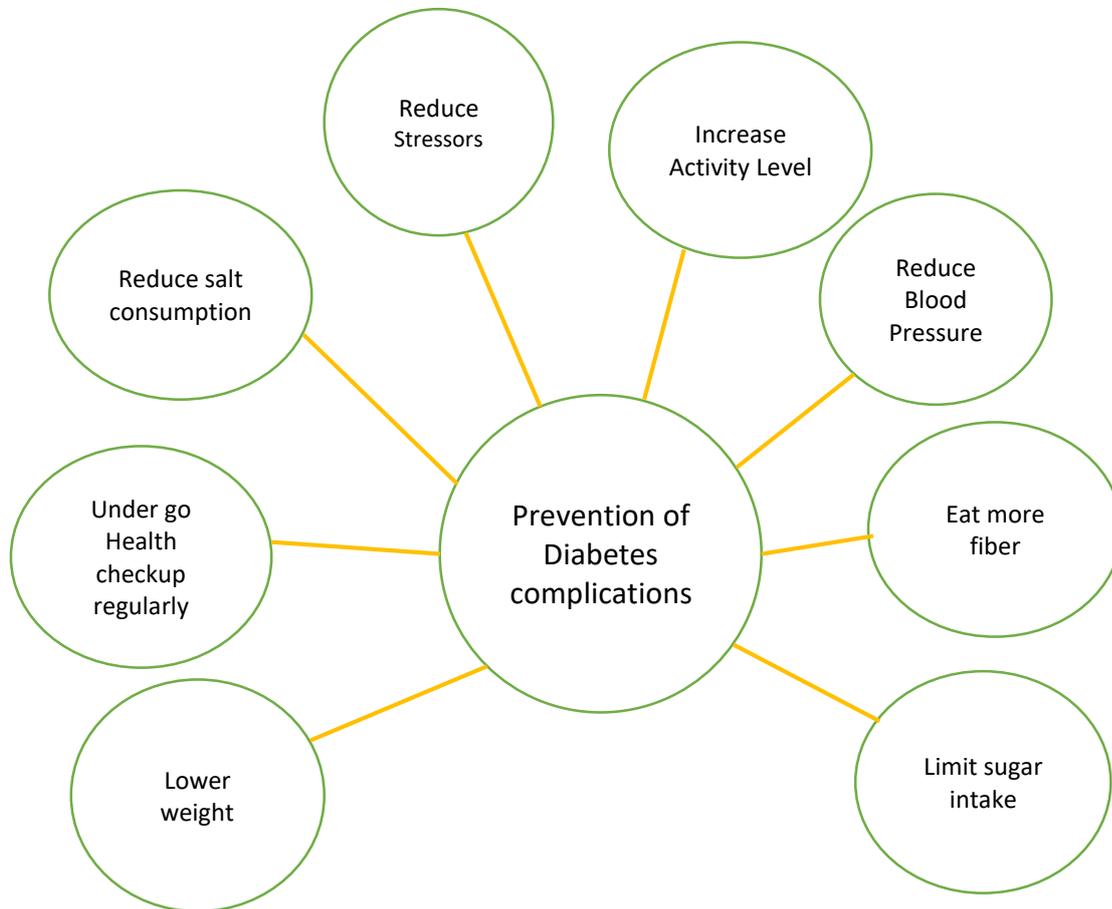
Reduction in proteinase secretion and alteration of membrane-associated properties of ATPase activity and other possible critical factors for anti-fungal activity of curcumin were observed[18].

ANTI DIABETIC ACTIVITY

Curcumin demonstrated anti-hyper glycemc and hypo cholesterolemic effects in type 2 diabetes as well as the protective effect against pancreatic injury mostly on β cells which secrete insulin, by its anti-oxidant and anti-inflammatory impact in a model of Streptozotocin (STZ) included pancreatic damage[19]. Some studies revealed that curcumin not only attenuates the complications that are directly made by diabetes, but also ameliorates the indirect complications caused by this disease.

For instance diabetic neuropathy, a micro vascular problem which occur mostly due to oxidative damage and inflammation, was shown to be improved after curcumin administration. Diabetic retinopathy, Nephropathy and cardio myopathy, the common complications of the long-lasting diabetes, were also ameliorated after curcumin consumption[20].

PREVENTION OF DIABETES COMPLICATIONS



ANTI-VIRAL ACTIVITY

Curcumin showed the anti-influenza activity viruses viz., PR8, H1N1, and H6NI. The results showed more than 90% reduction in virus yield. The plaque reduction test elicited the approximate EC_{50} of $0.47\mu m$ for curcumin against influenza viruses.

In H1N1 and also H6NI sub types, the inhibition haemagglutinin interaction reflected the direct effect of curcumin on infectivity of viral particles and this has proved by time of drug addiction experiment. Additionally, unlike amantadine, virus developed no resistance to curcumin. The methoxyl derivatives of curcumin also did not show noteworthy role in the hemagglutination[21]. These results proved the significant potential of curcumin for inhibition of influenza

ANTI-CANCER ACTIVITY

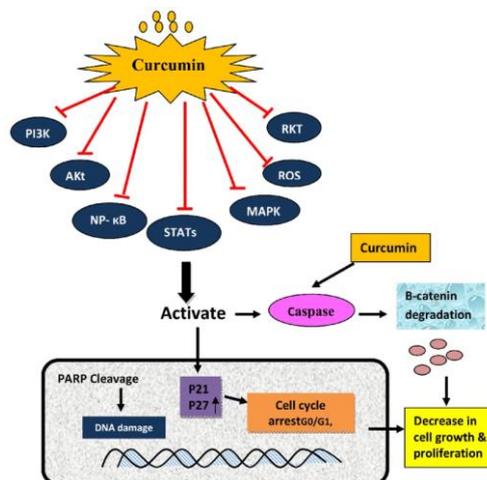


Figure 4: Mechanism of action of curcumin in Cancer.

Cancer, the second leading cause of death in humans, commonly treated by chemotherapy, radiation therapy, photothermic therapy, hyperthermia, etc. Curcumin nano formulations significantly internalize in cancer cells through endocytosis or receptors mediated pathway. In the presence of endocytosis inhibitors curcumin release is in active form in order to induce its biological effects[22]. Furthermore, curcumin nano formulations retained molecular targeting effects, even though curcumin is encapsulated in nano particles or nano carriers.

ANTI-ARTHRITIS ACTIVITY

Rheumatoid arthritis (RA) is a chronic inflammatory disease that is characterized by hyperplasia of the synovial fibroblasts. Curcumin is known to possess potent anti-inflammatory and anti-arthritic properties[23]. Curcumin treatment was compared with diclofenac sodium reference group. Curcumin group showed the highest percentage of improvement in overall rheumatoid arthritis scores and these scores were significantly better than the diclofenac sodium group. Treatment with curcumin was found to be safe and did not relate with any adverse events compared to diclofenac sodium group[24]. Properties like antioxidant, anti-proliferative, anti-inflammatory and immune suppressive activities of curcumin also helped in improvement of the RA.

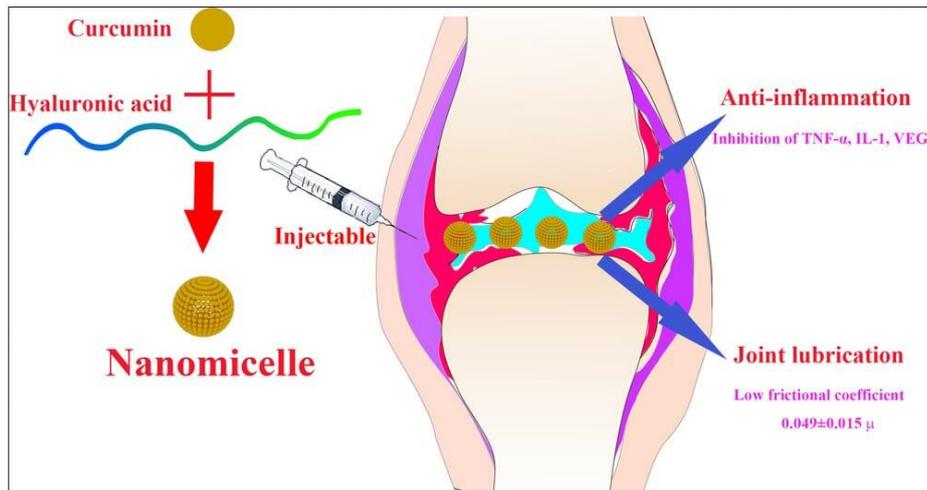


Figure 5: Curcumin Nano micelle -Improve the Efficacy of RA Therapy.

ANTI-OXIDANT ACTIVITY

In vitro stock showed that curcumin is an effective scavenger of free radicals and reactive nitrogen species and in other finding, the antioxidant activity was established by inhibition of controlled initiation of styrene oxidation[25]. The effective anticancer property of curcumin is attributed to its antioxidant effect that control DNA damage and free radical-mediated lipid peroxidation curcumin improves the activities of detoxifying enzymes such as glutathione-S-transferase (GST)[26].

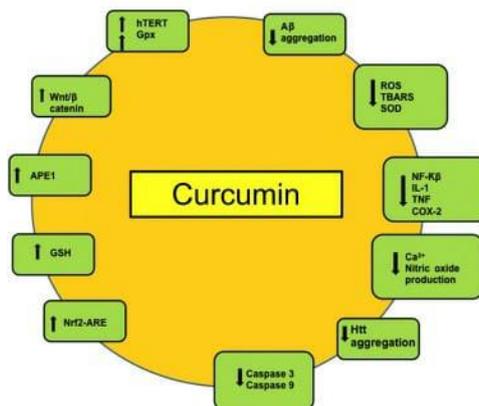


Figure 6: Mechanism of action of curcumin in antioxidant activity.

CURCUMIN FOR FOOD AND BIOTECHNOLOGICAL APPLICATIONS

Turmeric use as spice and food additive, widely used to ameliorate foodstuffs’ palatability and storage stability through its specific yellow colour, taste, and anti-oxidant potential. Curcumin species stability in aqueous solutions is p^H-dependent, with a cut-off point ranging from p^H-1-6. Its colour turns to red in charged state p^H<1 or p^H>7 and sunlight exposure accelerates curcumin degradation.

For nutritional purposes, curcumin is normally applied at a dose of 5-500mg/kg, depending on the food category. It is mainly used in dairy products, beverages, cereals, mustards, food concentrates, pickles, sausages, confectionery, ice cream, and meat, fish, eggs, and bakery products it is also added to season sauces, mayonnaise sauces, and butter. Curcumin is a good and cheap alternative to saffron, and known as “Indian saffron” in Europe. It is relatively inert to reactions with other ingredients, although may form salts with phthalates and citrates, and it is inert in reactions with phosphates, chlorides, and bicarbonates. It also proved that curcumin exhibits some antimicrobial effects, when added in food items viz; bread, bean curd, and cooked mutton etc and also showed increased oxidative stability in many food items as a natural preservative. Thus, curcumin suppressed lipid

peroxidation and seemed to be useful as scientists also stated that linoleic acid oxidation was much lower in the presence of curcumin, and the oxidant effect was about 80% when it was used as a dietary supplement. At the same dose, curcumin was able to double the antioxidant activity, due to the double carboxyl and hydroxyl groups.

Looking at Food Industry Goals and Consumers' Demands

Consumers' concerns on the use of artificial additives in food products have markedly increased. Indeed, various surveys have indicated that people are requiring more data on the health effects of food additives.

Food coloring agents are used at both commercial and domestic levels, with an increasing amount of natural food coloring agents being commercially produced as synthetic dye alternatives in foods. This occurs partly due to consumers' concerns about synthetic dyes, and on many regulatory bodies that have banned the use of some synthetic coloring agents. In addition, an increasing awareness among consumers is further fueling demand for curcumin over the forecast period, although it is also used in cosmetics and the pharmaceutical industry[27].

THERAPEUTIC APPLICATIONS OF CURCUMIN

Curcumin shown a wide range of therapeutic effects viz;

ANTI OXIDANT

Curcumin protects against free radical damage because it is a strong antioxidant. Water and fat-soluble extracts of turmeric and its curcumin component exhibit strong anti-oxidant activity, comparable to that of vitamins C and E[28].

ANTI INFLAMMATORY

It reduces inflammation by lowering histamine levels and possibly by increasing the production of natural cortisone by the adrenal glands. Oral administration of curcumin in instances of acute inflammation was found to be as effective as cortisone or phenylbutazone, and half as effective in cases of chronic inflammation. Its anti-inflammatory properties may be attributed to its ability to inhibit both biosynthesis of inflammatory prostaglandins from arachidonic acid and neutrophil function during inflammatory states[29].

ANTI MICROBIAL

Turmeric extract and the essential oil of *Curcuma longa* inhibits the growth of a variety of bacteria, parasites, and pathogenic fungi. Improvements in lesions were observed in the dermatophyte and fungi-infected guinea pigs, as at 7 days post-turmeric application, the lesions disappeared. Curcumin has also been found to have moderate activity against *Plasmodium falciparum* and *Leishmania major*[30].

CARDIOVASCULAR EFFECTS

Turmeric's protective effect on the cardiovascular system include lowering cholesterol and triglyceride levels, decreasing susceptibility of low-density lipoprotein (LDL) to lipid peroxidation, and inhibiting platelet aggregation[31]. These effects were noted even with low doses of turmeric. A study of 18 atherosclerosis rabbits administered low-doses (1.6-3.2 mg/kg body weight, daily) turmeric extract demonstrated decreased susceptibility of LDL to lipid peroxidation in addition to lower plasma cholesterol and triglyceride levels. Higher doses did not decrease lipid peroxidation of LDL, but cholesterol and triglyceride level decreases were noted, although to a lesser degree than with lower dose. Turmeric extract's effect on cholesterol levels may be due to decreased cholesterol uptake in the intestines and increase conversion of cholesterol to bile acids in the liver[32]

LOCAL EFFECTS

Fresh juice from the rhizome or a paste prepared from turmeric or decoction is often used as a local application as well as internally in the treatment of leprosy, snake bites, and vomiting associated with pregnancy[33].

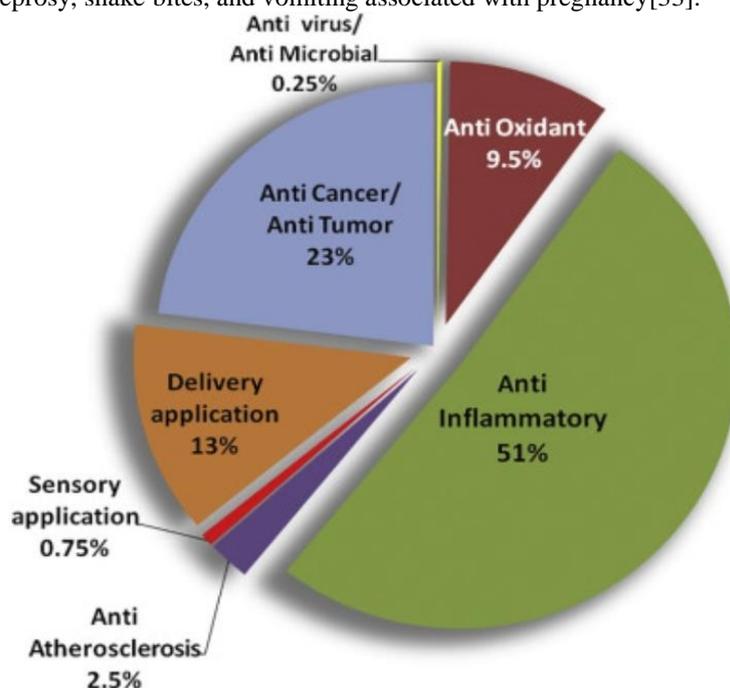


Figure7 :Various applications of curcumin and its derivatives.

THERAPEUTIC APPLICATIONS OF CURCUMIN NANOFORMULATIONS

CURCUMIN LOADING AND RELEASE

Curcumin is a less potent molecule than many clinically used chemotherapy drugs; therefore, its higher loading and encapsulation in nanoparticles may be useful because of its immediate availability to the cells when released from the nanoparticles. As found in literature, curcumin can be loaded up to 25w/w%. Each method of preparation determines its encapsulation efficiency and release phenomenon. Cellular micro environment plays a major role in degradation of nanoparticles and curcumin release from the nano formulations. These properties can be used as external stimuli for targeted delivery of curcumin.

SURFACE BIO-FUNCTIONALIZATION

Functionalizing a specific antibody, ligand, peptide, or aptamer to the surface of nanoparticles that promotes specific interaction with intended cells is highly relevant. Such formulations bind via receptor proteins to the specifically over expressing proteins on cell membrane. This creates an opportunity for targeted delivery of curcumin to diseased site.

CANCER

Following heart diseases, cancer is still the second leading cause of death in human. The most commonly used treatment modalities include surgery, chemotherapy, radiation therapy, targeted therapy, immunotherapy, hyperthermia, photothermic therapy, and other alternative therapies, traditionally, chemotherapy is highly recommended for both the solid and metastatic tumors. However, chemotherapy associated side effects are quite deleterious to normal/healthy issues/organs. Thus, curcumin and its nano formulations play a significant role in enhancing chemo/ radio sensitization and can act as treatment modality to provide a proper dose at the tumor site. This section deals with how curcumin nano formulations efficiently reduce the growth and metastasis potential of tumor cells or tumor burden. Curcumin nano formulations significantly internalize in cancer cells through endocytosis or receptor-mediated pathways in the presence of endocytosis inhibitors and release curcumin in active form in order to induce its biological effects[34].

CURCUMIN IN TRADITIONAL MEDICINE AND MODERN SCIENTIFIC APPLICATIONS

Curcumin [1,7-bis-(4-hydroxy-3-methoxy-phenyl)-hepta-1,6-diene-3,5-dione]

Traditional application	Modern application
Rheumatism	Alzheimer
Skin diseases	Parkinson's disease
Body aches	Multiple sclerosis
Wounds dressing	Epilepsy
Intestinal worms	Cerebral injury
Diarrhea	Mangolian Gerbils
Intermittent fevers	Cardiovascular diseases
Hepatic disorders	Allergy
Biliousness	Asthma
Urinary discharges	Bronchitis
Dyspepsia	Rheumatism
Inflammation(including colic inflammation)	Inflammation (including bowel disease and colitis)
Constipation	Renal ischemia
Leukoderma	Diabetes
Amenorrhea	AIDS
Eye infections	Gastrointestinal cancers
Burns	Liver cancers
Acne	Lung cancers
Sprains	Blood cancers
Asthma	Oral cancers
Swelling	Breast cancers
Allergy	Prostate cancers
Hyperactivity	Skin cancers
Diabetic	Colon cancers
Cough	Ovary cancers

TABLE 1: Traditional and Modern Applications of Curcumin.

Conclusion

Curcumin, an age-old traditional medicine found its usage in many traditions in the world. This article gives an overview of various pharmacological indications in which it is used and also discussed in detail about various studies carried out to establish the use of curcumin in various pathological conditions. This work demonstrates the safety profile, wide range usage and importance of curcumin in modern medicine, that too, in post covid scenario.

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