

CURCUMIN: PHARMACOLOGICAL ADVANCES AND DEVELOPMENT**Shashwat Garg, *Himanshu Joshi, Shweta Gupta and Mayuri Goyal**

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ABSTRACT

Now a days there is a growing interest in herbal medicines. Curcumin is a spice which is of bright yellow color and its derived form rhizome of curcuma longa Linn. It belongs to the family zingerberaceae. It has been proven that curcumin is a highly pleiotropic molecule which can be a modulator of intracellular signaling pathways that control cell growth, inflammation, and apoptosis. Curcumin may be a potential candidate for the prevention and treatment of some diseases due to its anti-oxidant, anti-inflammatory. The most common method of isolation of curcumin is extraction with organic solvents mainly using ethanol and by various methods like Soxhlet, ultrasonic and microwave extraction. It has various properties like anti-inflammatory, chemoprotective, gastro protective and anti-cancer. It affects the neuro system and also it is one of the most investigated bioflavonoids. We present the concise knowledge on curcumin and its therapeutic effects.

KEYWORDS: It belongs to the family zingerberaceae.**INTRODUCTION**

Turmeric is also known as *Curcuma longa* is a medicinal plant used in Ayurveda, Siddha and Unani medicine as home remedy for various diseases. Curcumin is botanically related to ginger known as Zingiberaceae family. It is a perennial plant having a short stem with large oblong leaf and ovate, bears, pyriform or oblong rhizomes. They are often branched and brownish- yellow in color.^[1]

Curcumin is the active ingredient in the herbal remedy and it is also used as a dietary spice known as turmeric. Curcumin has a very long history of administration in traditional medicine of China, India and Iran and it has also been used in different folks for the treatment of many diseases such as diabetes, liver disease, rheumatoid diseases, atherosclerosis, infectious diseases and different types of cancers.^[2] Curcumin is one of the most researched bioflavonoids today and number of studies have also confirmed that its antioxidant, anti-inflammatory, anti-cancer, chemoprotective, gastroprotective, and many other health properties.^[3] The use of curcumin became more popular when it was found that it has a various therapeutic agent for various illnesses. In the Ayurvedic system of medicine, curcumin is used as a tonic and as a blood purifier.^[4] Commercially, curcumin can be sold either fresh without powdered form or as dried powder. Dried curcumin powder is more often sold all around the world but the price varies and it depends on many factors including quality that is moisture content, appearance (color), and

phenolic contents.^[5] Antioxidant and anti-inflammatory effects of the curcumin have been assessed in various in vitro systems and in experimental animal models.^[6]

Biological importance of curcumin

Curcumin has many biological activities which increases the mucin secretion and also act as a gastric protection. It has many beneficial effects on the intestine.

Curcumin decreases the density of lipoprotein and it also significantly affects the plasma and total cholesterol level in liver along with an increase of alpha-tocopherol level. It clearly shows that the in vivo interaction between curcumin and alpha tocopherol may increase the bioavailability of vitamin E and it also decrease the cholesterol level. Curcumin binds with egg and soy-phosphatidylcholine, which binds divalent metal ions that makes the antioxidant activity. Induced liver damage is significantly decreased by the curcumin treatment and the arachidonic acid level gets increased with increase in curcumin intake.

Curcumin also shows the protection against ulcerogenic effects of phenylbutazone in guinea pigs at a dose of 50 mg/kg. Anti flatulent activity of curcumin was observed in both in vivo and in vitro experiments in the rats. Sodium curcuminates from turmeric acts as an antispasmodic activity and it is observed in guinea pig ileum.

Curcumin have enhancing capacity of intestinal lipase, sucrase and maltase activity. It also has the capacity to reduce the pathological effect and it also protects from the damage which is caused by myocardial infarction. Curcumin increased the Ca^{2+} transport and it's slippage from the cardiac muscle sarcoplasmic reticulum which makes to raise the possibility of medicinal interventions to correct the defective Ca^{2+} homeostasis in the cardiac muscle. It was observed that curcumin has a significant reduction of cholesterol in the hypercholesteremi rats. The antioxidant activity present in curcumin makes the vascular dementia reduced on the nervous system by curcumin and its manganese complex.

Turmeric oleoresin effects the change in gene expression and were observed in mice and they are considered to be the mechanism by which the turmeric oleoresin affects the control of both blood glucose levels and abdominal adipose tissue masses. All of these results above shows that the use of whole turmeric oleoresin is more effective than the use of either curcuminoids or the essential oil alone.^[7]

SOLUBILITY OF THE CURCUMIN

Oral bioavailability of a drug depends on its solubility and dissolution rate and dissolution may be rate determining step for appearance of medicinal effect, therefore efforts are needed to increase dissolution of drug with limited water solubility which is often needed. Many methods are also available to improve these characteristics, including salt formation, micronization and addition of solvent or surface active agents is. Solid dispersion (SD) is one of these methods which involves a dispersion of one or more active ingredients in an inner carrier or matrix in solid state is prepared by melting, dissolution in solvent or melting solvent method. A huge investigation has exposed that turmeric and curcumin has an extensive variety of curative property such as antiinflammatory, antibacterial, antifungal, anticancer antispasmodic, antioxidant, antiamoebic, anti HIV, antidiabetic, antifertility etc. Curcumin has a golden color attained by *Curcuma longa* is been used from the time immemorial as a nutritional complement, coloring means, spice and also for therapeutic the purpose. It is also accounted that the curcumin is safe and can be used up to 8g/day.^[8]

THERAPEUTIC EFFECTS

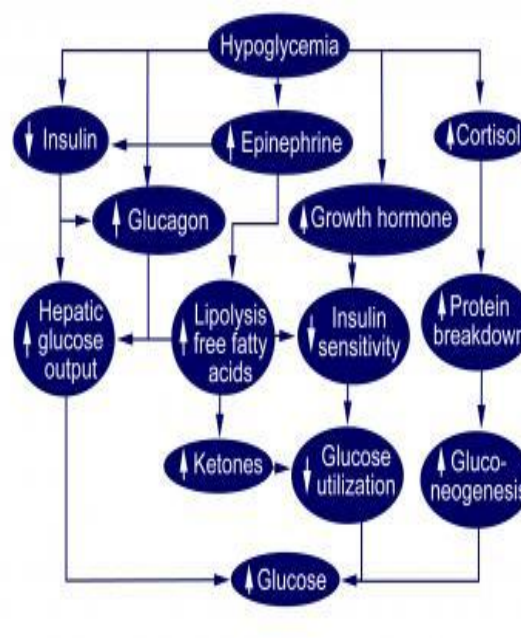
Hypoglycemic effects

Curcumin and its analogs have been synthesized to improve its hypoglycemic efficacy which helps for the diabetic people. For an instance, a novel curcumin derivative (NCD) was developed through the covalent modification of the curcumin molecule on sites remote from its natural functional groups.

This novel curcumin derivative (NCD) was tested on the diabetic rats to determine whether it exhibits a

hypoglycemic effect. The results clearly showed that it lowered the plasma glucose by 27.5 percent and increased plasma insulin by 66.67 percent.

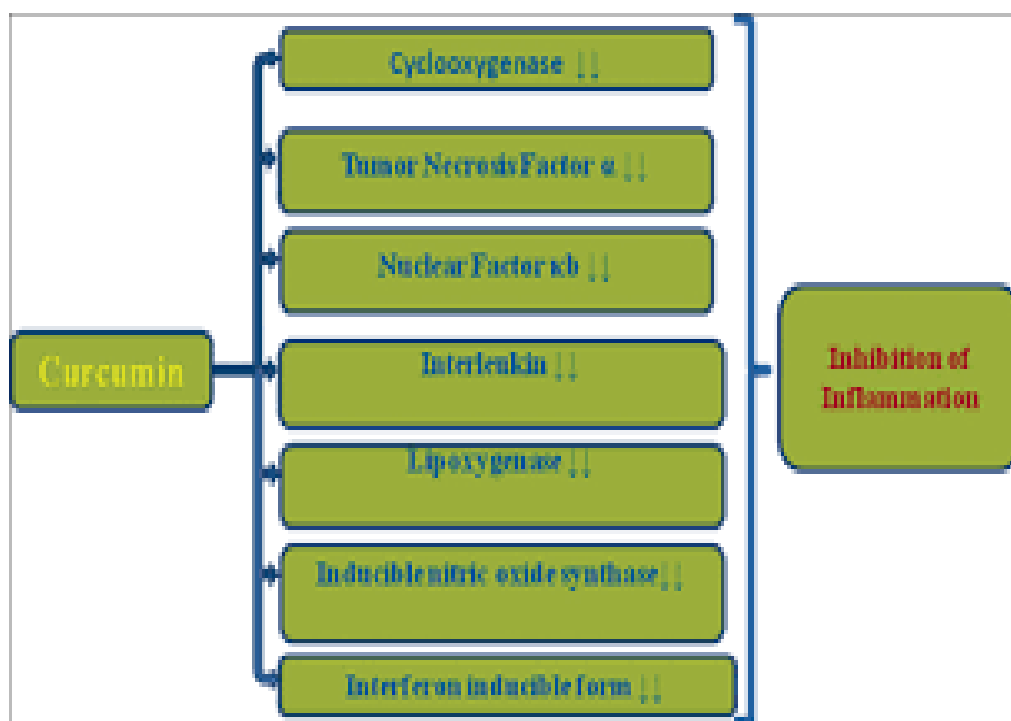
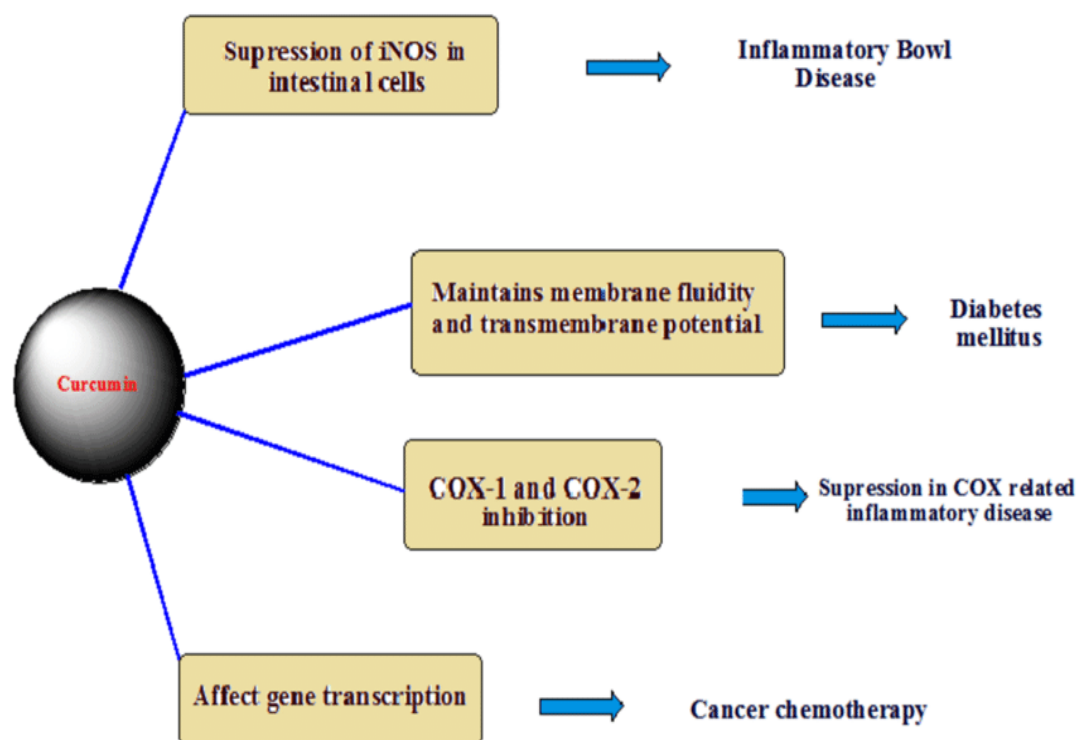
Later, it was observed that this novel curcumin derivative was partially mediated by induction of the HO-1 gene. Another curcuminoid derivative, bis methane, inhibited these levels of plasma glucose in the diabetic rats. This is clearly evident that curcumin derivatives exhibit antidiabetic activities.^[7]



Anti-inflammatory effects

Curcumin was found to possess a miraculous power in anti-inflammatory cycle in the body. Inflammation is a very necessary process for fighting infections. Various experimental and pharmacologic trials have been signified it's efficacy as an anti-inflammatory agent. A lipophilic derivative and hydrophilic derivatives of curcumin such as diacetyl curcumin and diglutaryl curcumin also showed in vivo to have an analgesic and anti-inflammatory properties.

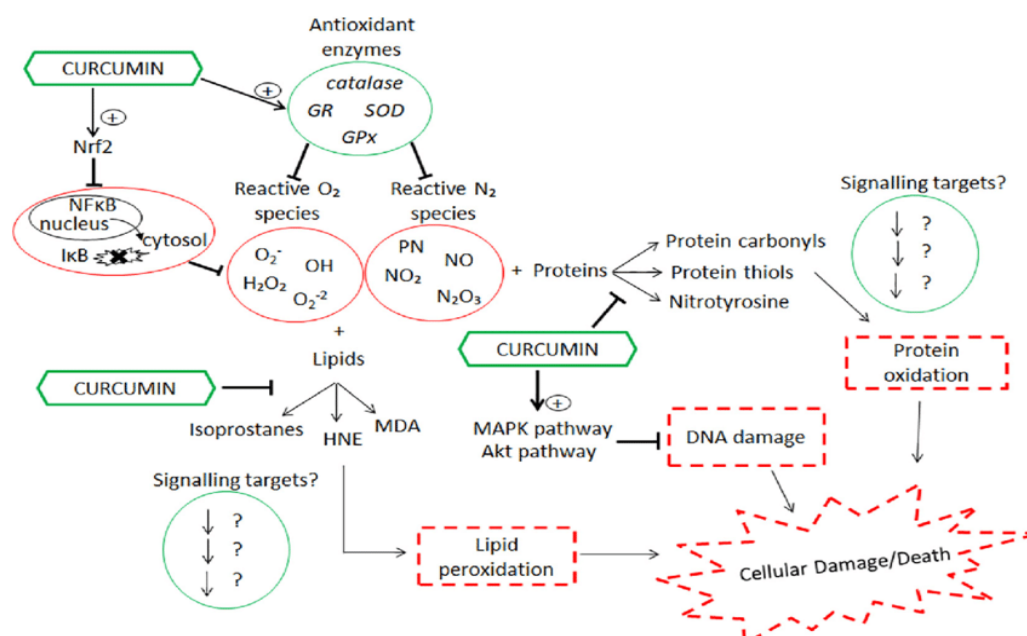
Curcumin's this property has been shown to be mediated through down-regulating the activity of various signaling mediators including downregulation of COX-2 activity, mitogen-activated and inhibiting the generation of TNF-alpha, IL-1, -2, -6, -8, -12, and 5. Many of the activities associated with curcumin are related to its ability to suppress the acute and chronic inflammations. Curcumin analogs plays a very potential role to inhibit the inflammatory factors.^[9]



Antioxidative Effects

Curcumin is known for its antioxidant and radical properties. The discovery of the antioxidant properties of curcumin explains a lot of its various pharmacological activities. Curcumin shows various antioxidant properties as a food additive. Curcumin not only exhibits antioxidative and free radical scavenging properties, but also enhances various activities of other antioxidants, like superoxide dismutase, catalase, and glutathione peroxidase. Oxidative stress plays a major role in the

pathogenesis of many diseases including cancer, diabetes, cardiovascular diseases, neuronal cell injury, and hypoxia and many experimental models, mainly in the field of injuries of nervous system. Oxidative stress and the loss of vitamins like C and E during sleep in an area with little or no gravity which shows that curcumin reduces the loss of these vitamins. Curcumin also protects the renal cells and neural glial cells from oxidative stress.^[10]

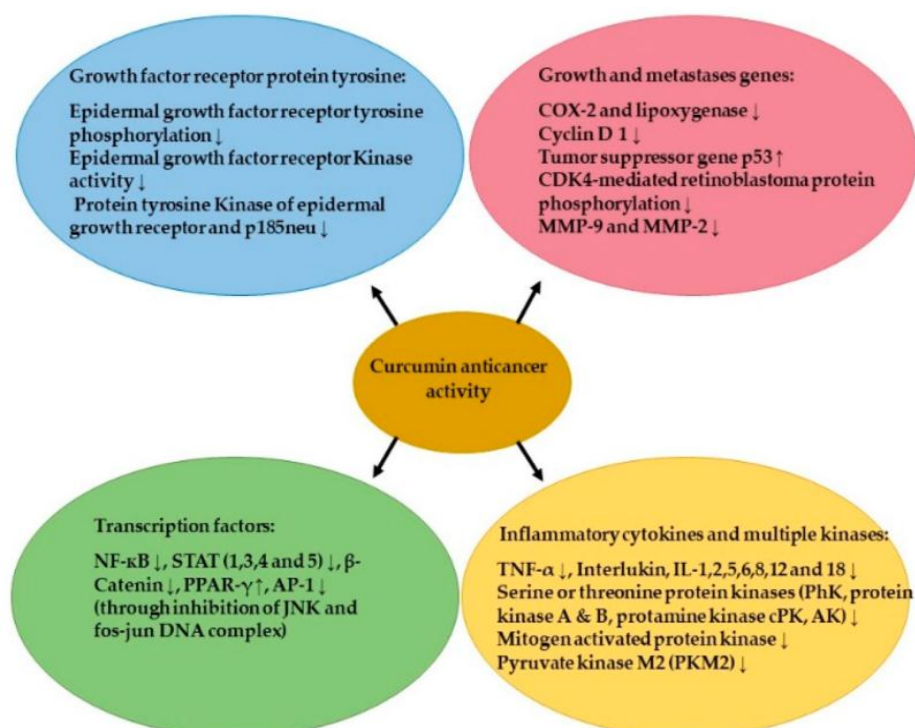


Immunomodulatory Effects

The immune system has evolved to various specialized cells, and makes soluble molecules that are organized into a number of organs and tissues including bone marrow and thymus as the central lymphoid organs and lymph nodes, spleen and also mucosal lymphoid tissues, as peripheral ones. Current traditional, Indian medicine claims that the use of its powder against biliary disorders, anorexia, coryza, cough, diabetic wounds, hepatic disorder, rheumatism, and sinusitis. Curcumin inhibits the neutrophil activation, and suppresses the mitogen-induced proliferation of blood mononuclear cells, and inhibits mixed lymphocyte reaction (MLR) and proliferation of smooth muscle cells in vitro.^[11]

ANTI Cancer

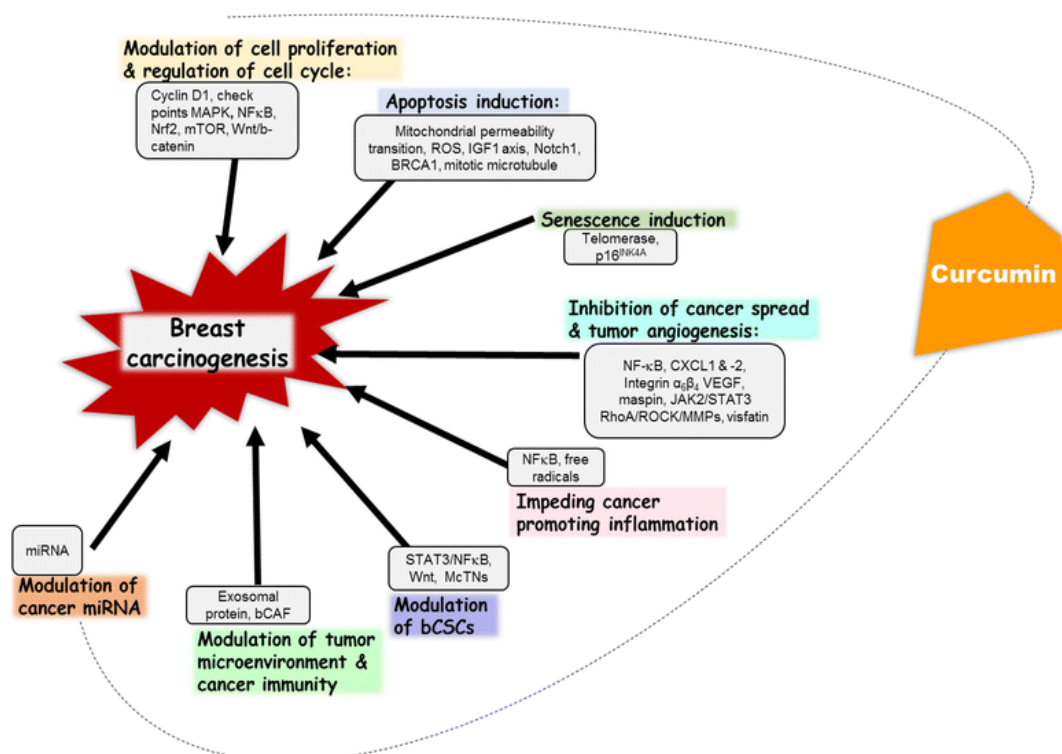
Cancer is the second most life-threatening disease and it is one of the main public health problems worldwide. In 2018, there were around 1.73 million new cases of cancer and more than 609,000 deaths occurred due to cancer in the United States alone. Despite the tangible advances in cancer therapy, the reported incidence of the disease and the mortality have not been declined in the past 30 years. There are many common strategies for targeting specific cancer cells to inhibit tumor development, progression and metastasis without causing severe side effects in the body. Curcumin has been shown to display chemotherapeutic as well as the chemo preventive effects in different types of cancers.^[12]



Breast Cancer

Breast cancer has shown an alarming record as a leading cause of death among females in all over the world mainly in United States. Its rate in China and other Asian countries is also getting increase day by day. Despite the radiation therapy, chemotherapy and endocrine therapy, the recurrence rate of breast cancer is seeing. Chemotherapy has been the most frequently used treatment for breast cancer and also for other cancers. However, some normal cells also gets destroyed by this

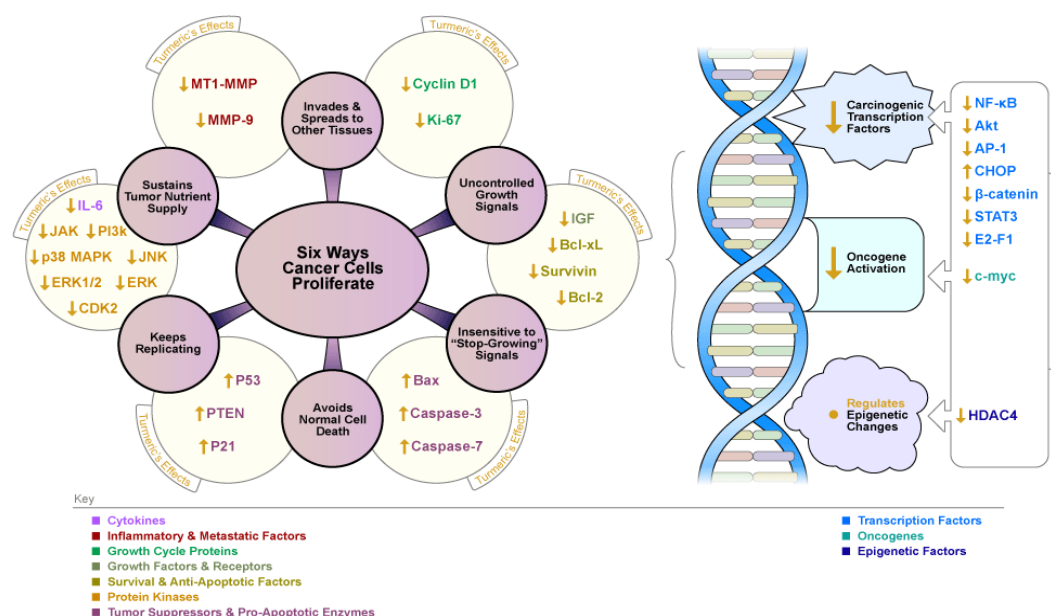
method of treatment. They have wide range of biological activities and low toxicity in animal models, due to that some natural products have been used as alternative treatments for cancers including breast cancer. Curcumin possesses anti-proliferative and anti-carcinogenic properties in a wide variety of cell. Curcumin, either alone or in combination with other agents of anti cancer, can efficiently induce apoptosis. This is evidenced by its inhibitory effects on the growth of a number of tumor cells.^[13]



BRAIN CANCER

The incidence rate of central nervous system (CNS) tumors, including brain tumors, has been predicted to be increased by 6% in the UK between 2014 and 2035. Glioblastoma (GBM), and it is the most common malignant brain cancer in humans, accounts for about 15% of all CNS tumors. In the treatment of brain tumors

and GBM (Glioblastoma) surgical intervention and radiation therapy are being limited as they can't do the infiltration of cancer cells into the healthy brain, leading to damaging effects after treatment. Therefore, there are alternative therapies using naturally derived compounds such as curcumin with less side effects rather than the conventional treatments are receiving more attention.^[10]



ANTIBACTERIAL EFFECTS

Curcumin has also been shown to have a *in vitro* antimicrobial potential against a wide range of microorganisms including fungi as well as several Gram-positive and Gram-negative bacterial. Recently, it has been showed that curcumin suppresses the adherence of *Streptococcus* mutants to human tooth surfaces and extra-cellular matrix protein. Researches has further highlighted that curcumin also have a synergistic effect with important antibiotics such as cefixime, vancomycin and tetracycline against *Staphylococcus aureus* (*S. aureus*). However, very few studies have demonstrated that the mechanism of antibacterial activity of curcumin I which seems to differ depending on the strain being studied. Further, studies have also demonstrated that the antibacterial activity of curcumin against *Bacillus subtilis* occurs through the inhibition of bacterial cell proliferation by blocking the assembly dynamics of FtsZ in the Z ring. In the case of *Pseudomonas aeruginosa* (*P. aeruginosa*) infection, curcumin shows to have anti-infective activity through affecting virulence, quorum sensing and biofilm initiation. Moreover, these mechanisms have not been confirmed in the case of other bacterial genera, hence thses mechanism could not be generalized for all of the bacteria. Therefore, a detailed study on antibacterial mechanism of curcumin, in which it should include a large number of bacteria from different genera is required. Due to the increase of resistance in the bacteria like Grampositive and Gram-negative bacteria, there is an urgent need to identify and assess the alternative antimicrobials, including those from plant materials with a low human cytotoxicity. In an experiment it is found that Curcumin I showed no toxic effect on human health even when taken at doses as high as 8 g day⁻¹. Considering these factors, in the present study, it is being investigated that the detailed antibacterial activity of curcumin I (the major component of commercial curcumin) against two Gram-positive bacteria, namely, *S. aureus* and *Enterococcus faecalis* (*E.*

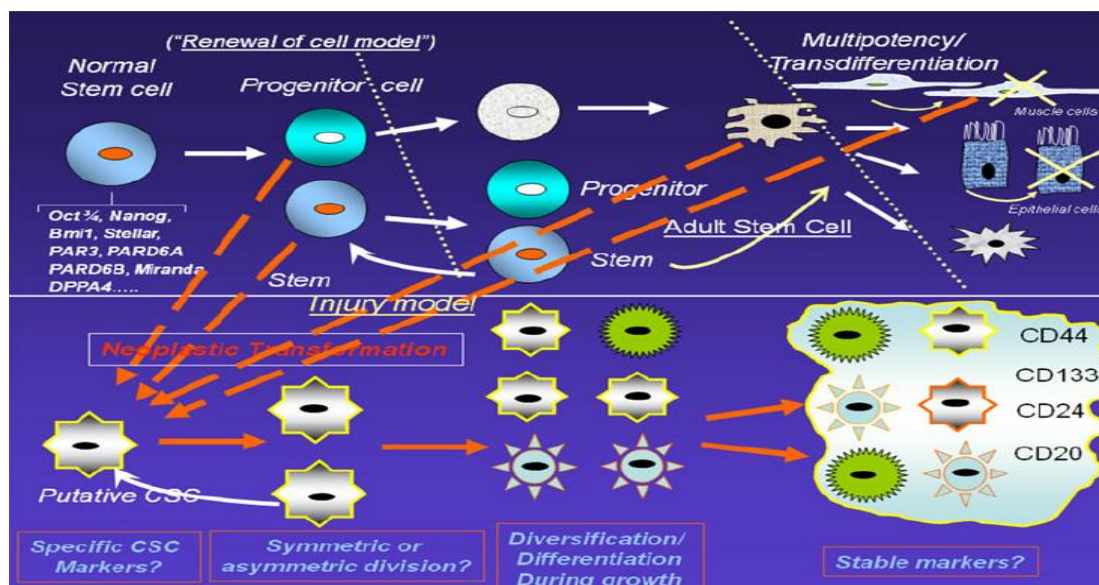
faecalis), and two Gram-negative bacteria, namely, *Escherichia coli* (*E. coli*) and *P. aeruginosa*. The study is being extended to explore the bacterial membrane lysis induced by curcumin I against the organisms from the mentioned bacterial groups. The membrane lysing properties of curcumin were further viewed through various microscopy like scanning electron microscopy and confocal fluorescence microscopy.^[14]

Effects of curcumin on cancer and normal stem cells

Curcumin shows to have numerous cytotoxic effects on cancer stem cells (CSCs). This is due to its suppression of the release of cytokines, particularly interleukin (IL)-6, IL-8 and IL-1, which stimulate CSCs, and also its effects at multiple sites along CSC pathways, such as Wnt, Notch, Hedgehog and FAK. In spite of its multiple actions which targets the CSCs, curcumin has little toxicity against normal stem cells (NSCs). It may be due to curcumin's different effects on CSCs and NSCs. The use of cytotoxic therapies remains the standard treatment for patients who are suffering from metastatic cancer. Efficacy of these treatments are limited, with recurrence common. According to the cancer stem cell paradigm, cancers does contain the distinct subpopulations of the cancer stem/progenitor cells (CSCs) characterized by self-renewal mechanisms and resistance to conventional treatments. When CSCs are transferred to an immune-deficient mouse, then these cells gets reconstitute the original cancer in the animal. Even a small number of stem cells (as few as 100) can be effective in bringing te transplantation process. However, tumors depleted of stem cells does not grow as a xenografts. These CSCs have been shown to be resistant to the various therapy like chemotherapy, radiation and hormone therapy. For this reason, metastases from solid tumors, which particularly, will re-appear even after initially successful treatments and prolonged periods of complete remission. Further, an unintended consequence of induced cancer cell death is the sign of release of inflammatory

cytokines, which can stimulate replication of CSCs. The percentage of CSCs in the cancer has been shown to increase in patients who are receiving neoadjuvant chemotherapy. Thus, an “equilibrium” may be formed where the chemotherapy induced tumor cell death results in increased the stimulation of tumor growth. In addition,

the cytokines secreted during induced cancer cell death which results in resistance to cytotoxic agents, so that the metastases and when they occur, it may be refractory to therapy. This suggests, for therapy to be effective on a consistent basis and it must eliminate both CSCs and non-stem cell cancer cells.^[15]



CONCLUSION

The beneficial effects of curcumin are traditionally achieved through dietary consumption, even at low levels, over long periods of time. A precise understanding of effective dose, safety, and mechanism of action is required for the rational use of curcumin in the treatment of human diseases. Curcumin is used for their various medicinal properties like anti-inflammatory, antioxidative etc. Curcumin is also been used for its therapeutic effects particularly in traditional and modern ways. The most noticeable therapeutic influences of curcumin as anti-oxidant, anti-inflammatory through its regulatory impacts on molecular targets involved in development of cancerous cells. Future therapeutic approaches could rely on the ability of curcumin to prevent the oxidative stress, inflammation and also in the immunomodulatory disorders. Curcumin, has the ability to affect a various range of molecular targets and it is an excellent safety profile.

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