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NANO-CURCUMIN: A USEFUL CANDIDATE IN THERAPEUTIC APPLICATIONS

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ABSTRACT

Curcuma longa is a significant medicinal and spice plant in Asia. Curcumin (diferuloylmethane) is a hydrophobic bioactive ingredient extracted from the rhizome of Curcuma longa. It has garnered considerable attention in recent years due to the breadth of its biological and pharmacological effects. However, its low solubility in water, low bioavailability, and rapid metabolism all pose significant limitations to its successful therapeutic applications. Thus, researchers have attempted to enhance curcumin's biological and pharmacological activity and overcome its disadvantages through the use of efficient delivery systems, most notably nanoencapsulation. Thus far, research efforts and data from the available literature indicate that nanoscale formulations of curcumin (Nanocurcumin) have a promising potential; they enhance all of curcumin's biological and pharmacological benefits in a way that was previously not possible. Numerous techniques have been developed for the synthesis of nanocurcumin, each with its own set of advantages and characteristics. Ionic gelation and antisolvent precipitation are the two most widely used and effective techniques. Numerous curcumin nanoformulations have been developed to increase curcumin delivery and thus overcome curcumin's low therapeutic efficacy. However, because the majority of curcumin nanoformulations remain at the concept stage, several questions and challenges remain before nanocurcumin can be recommended as a promising candidate for therapeutic applications. We discuss the various curcumin nanoformulations and their implications for various therapeutic applications, as well as the status of ongoing clinical trials and patents, in this review. Additionally, we discuss the research gap and future directions necessary to advance curcumin as a potential therapeutic candidate.

KEYWORDS: Curcumin, curcuma longa, nanocurcumin, water solubility, bioavailability.

1. INTRODUCTION

Curcuma longa commonly referred to as turmeric is an ancient perennial herb belonging to the family Zingiberaceae and native to India. Curcuma has developed by incessant cross-breeding and selection. To date, over 100 known species are reported in the species of Curcuma.[1] Curcumin, 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadien-3,5-dione, is a lipophilic molecule that rapidly permeates cell membrane.[2] Typical extract of *Curcuma longa* L. contains the structures I to III: (I) diferuloylmethane/ curcumin (curcumin I, 75%), (II) desmethoxycurcumin (curcumin II, 20%), and (III) bisdemethoxycurcumin (curcumin III, 5%)[3, 4] (Figure 1). Curcumin is an active ingredient in the herbal remedy and dietary spice turmeric.[5] It has a long history of administration by different folks of China, India, and Iran for the treatment of many diseases such as diabetes, liver diseases, rheumatoid diseases, atherosclerosis, infectious diseases, cancers, and digestive disorders such as indigestion, dyspepsia, flatulence, and gastric and duodenal ulcers.[6,7] Besides, the widespread Curcuma longa (syn. Curcuma domestica), Curcuma aromatica, and Curcuma xanthorrhiza are other common species. It is grown in tropical and subtropical areas of the world, extensively cultivated in Asian countries, viz., India, Burma, Bangladesh, China, Indonesia, Japan, Taiwan, Thailand, and Vietnam. Curcuma species exhibit inter and intraspecific differences in the biologically active principles combined with morphological differences in the above-ground vegetative and floral characteristics and the under-ground rhizome characteristics. Curcuma has a strong relationship with the socio-cultural life of the people of Asia, using it as a medicine, nutritional spice, and food preservative.[8] Curcumin contains many valuable biological properties (Figure 2) and molecular mechanism of these properties are given in Table 1. It is capable to bind and obstruct different proteins, metals, growth factors, transcription factors, receptors, enzymes, and other important biomolecules directly and indirectly.[9] So far, many researchers have investigated the molecular targets of curcumin and identified the direct targets include metal ions, inflammatory molecules, protein kinases/ reductases, proteasomes, DNA methyltransferase 1, carrier proteins, and cell survival proteins. The indirect targets comprise enzymes, transcription factors, adhesion molecules, mediators of inflammation, receptors, growth factors, proteins regulating the cell cycle, and proteins for cell survival.[10] Several molecular targets mediated by curcumin are summarized in Figure 3. Curcumin is a pleiotropic molecule that can interact with several inflammatory-related molecular targets.[11] It controls the inflammatory response by decreasing the activity

of inducible nitric oxide synthase (iNOS), lipoxygenase (LOX), phospholipases A2 (PLA2s), and cyclooxygenase-2 (COX-2) enzyme pathway that obstructs the prostaglandin synthesis and pro-inflammatory leukotrienes and essential inflammatory response mediators.[12] Curcumin inflammatory response is closely related to the arachidonic acid pathway for eicosanoid biosynthesis, which produces a host of reactive lipid products such as prostaglandins, thromboxanes, leukotrienes, and prostacyclins. Curcumin downregulated the activities of LOX and COX-2 at the transcriptional level and through inhibition of the posttranslational enzyme that leads to a reduction in arachidonic acid metabolism. Also, curcumin has been shown to obstruct the biosynthesis of prostaglandin E2 by direct inhibition of the microsomal prostaglandin E2 synthase-1 enzyme.[13]

Table 1: Biological properties and their molecular mechanism of curcumin or nanocurcumin.

S. No	Biological properties	Molecular mechanism
1	Anti-inflammatory	Curcumin control the inflammatory response through decreasing the activity of cyclooxygenase-2 (COX-2), lipoxygenase (LOX), phospholipases A2 (PLA2s) and inducible nitric oxide synthase (iNOS) enzymes pathway that obstructs the prostaglandin synthesis and pro-inflammatory leukotrienes and essential inflammatory response mediators
2	Anticancer	STAT3 and NF-κB signaling pathways play major role in cancer growth, curcumin effectively obstruct the activity of STAT3 and NF-κB. Besides, curcumin obstructs cancer formation, migration, and invasion by control the expression of Sp-1 and its housekeeping genes.
3	Antiamyloid	Curcumin regulates amyloid beta (Aβ) metabolism and inhibits Aβ aggregation and as well as disaggregates to form fibrillar Aβ16, Aβ40, and Aβ42 many ways to produce strong anti-amyloidogeni effects.
4	Antioxidant	Curcumin can ability to scavenge free radicals (i.e., ROS and RNS and also modulate the enzymes (GSH, catalase, and SOD) activity to neutralize the free radicals. Besides, curcumin also obstructs ROS-producing enzymes (i.e., lipoxygenase/cyclooxygenase).
5	Antimicrobial	The potential mechanism underlying curcumin antimicrobial activity related to FtsZ that is vital cell division initiating protein.
6	Antifibrosis	Curcumin prevent migration, collagen production, and proliferation abilities of fibroblast through modulating the expression of transforming growth factor (TGF)-β and angiotensin signaling (Ang).
7	Antidiabetic	The mechanism through which curcumin suppresses advanced glycation end products (AGEs) formation is suggested to involve the suppression of AGE receptor (RAGE) expression through the activation of peroxisome proliferator-activated receptor gamma (PPARγ) activity and increase in glutathione synthesis. Increasing secretion of insulin from pancreatic cells, reduces insulin resistance.

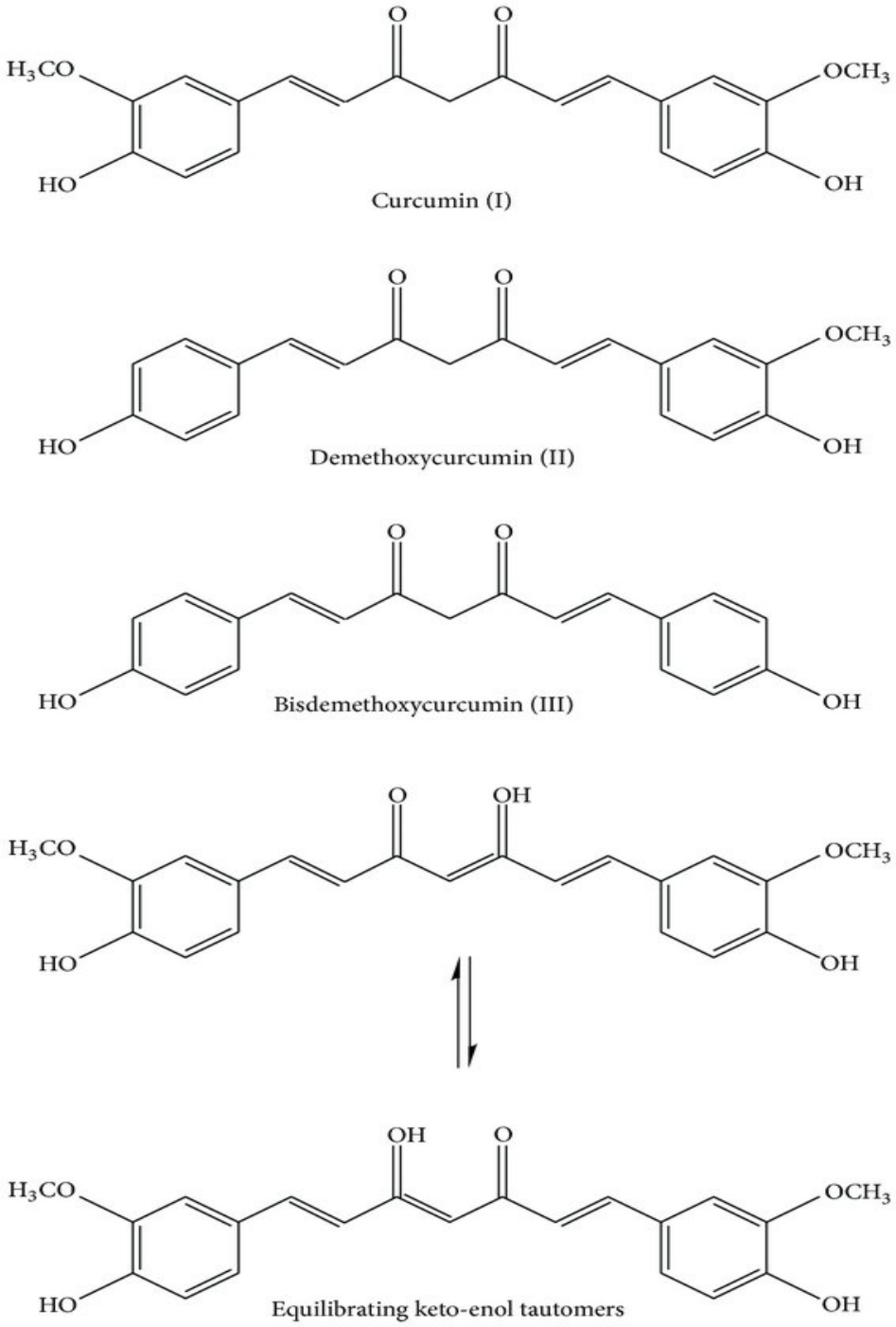

Figure 1: Curcumin I, II, and III (curcumin, demethoxycurcumin, and bisdemethyoxycurcumin) and curcumin keto-enol tautomers.

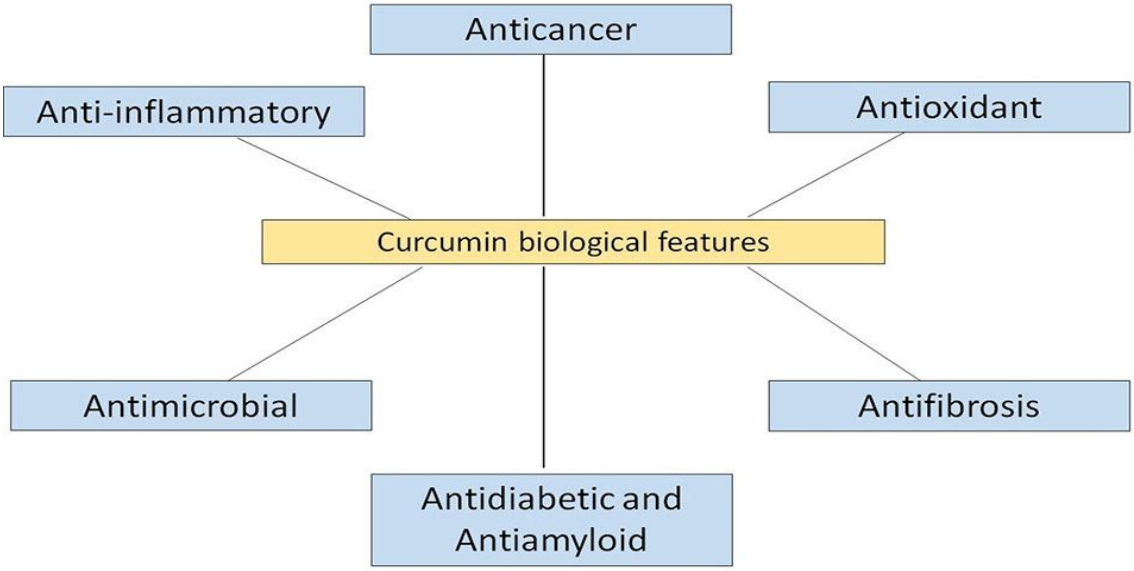

Figure 2: Different functional and biological features of curcumin or nanocurcumin.

2. Uses of Nanocurcumin

2.1. Wound Healing

Curcumin is basically a substance which is derived from the nature itself having innate properties and abilities of fighting against the microbial infections as well as healing the wounds. The overall process of healing of wounds is a dynamic as well as complex process comprising of various phases such as inflammation, proliferation, and maturation. However, the aqueous solubility of curcumin is very poor, and the curcumin's profile of rapid degeneration deters the usage of curcumin. However, with the help of encapsulation of curcumin by nanoparticles, these kinds of hindrances can be successfully overcome, enabling topical delivery of the agent in an extended way. A schematic representation of the study of[14] is in Figure 4. It can be observed that the infected burn wounds which were treated with curcumin nanoparticles statistically showed a significant decrease in the counts of bacteria on the 3rd day and also the 7th day as compared to the control burn wounds which were not treated by the curcumin nanoparticle. It was also observed that the administration of nanocurcumin topically helped in faster healing of wounds than that of those which were not treated with nanocurcumin. Apart from the faster closure and healing of the wounds, the qualitative assessment in the study revealed the fact that the wounds treated by nanocurcumin showed formation of the granulation tissue in a better way, and also the re-epithelialization occurred earlier as compared to other wounds which were untreated. Nanocurcumin has an overall multifaceted impact on the healing of wounds and mostly on the proliferative phase it acts by increasing the deposition of collagens, production of fibronectin, as well as re-

epithelialization. However, in this study, the toxicity of the nanocurcumin when applied topically in chronic wounds and their absorption and accumulation inside the internal organ has not been studied extensively. The curcumin solid lipid nanoparticles extensively exhibit better solubility properties than that of native curcumin.[15] It helps in the downregulation of the pro-inflammatory mediators which are induced by polysaccharides (LPS) such as that of prostaglandin E2, nitric oxide (NO) etc. by the process of causing obstruction to the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-_B) activation in the murine macrophage of RAW264.7. The curcumin nanopolymers are used extensively in delivering the curcumin drugs effectively as it helps in improving the oral bioavailability along with better solubility of curcumin. Kartikeyan's article.[16] pointed out that the nanocurcumin polymers showed solid wound healing properties than that of free curcumin. On the other hand, ref.[17] showed that the nanocurcumin with solid dispersions helped in considerably improving the wound healing of the vaginal area because of improved bioavailability of the curcumin drugs which are very poorly soluble in water. The nanocurcumin formulation of liposomes have an anti-inflammatory effect against 2-hydroxyethyl methacrylate present in the pulp stem cells of human teeth thereby improving the wound healing and dental care quality.[18]

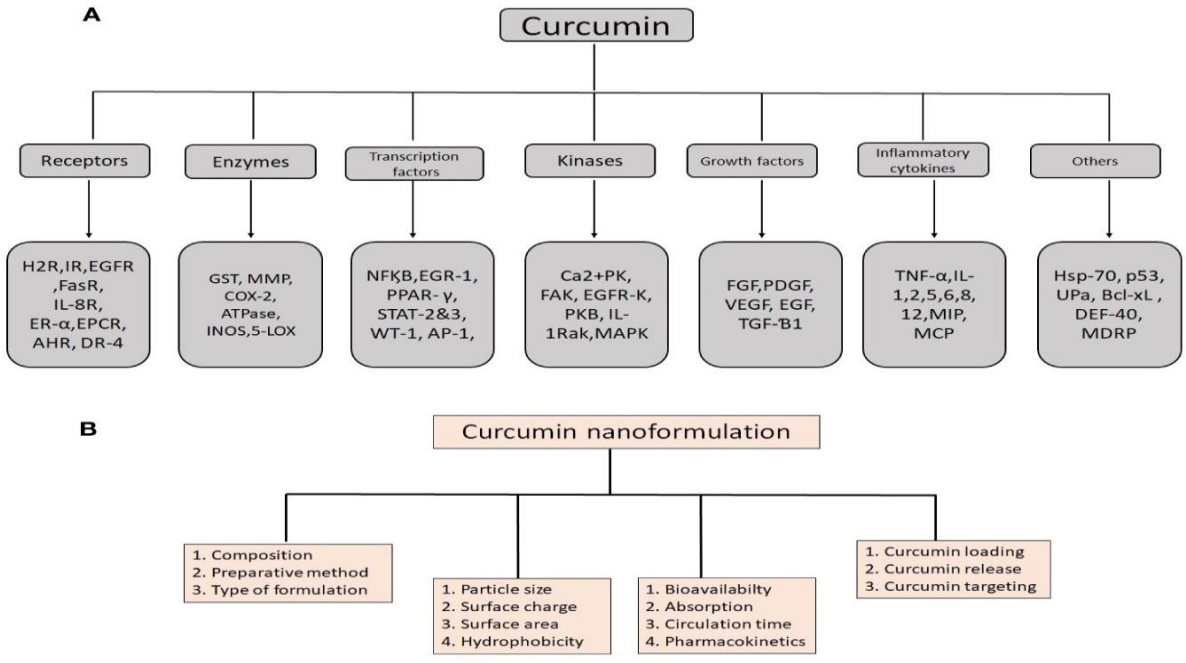

FIGURE 3: Details of molecular targets mediated by curcumin (A) and important physico chemical properties and their role in biological functions to remember when producing an effective nanoformulation of curcumin (B).

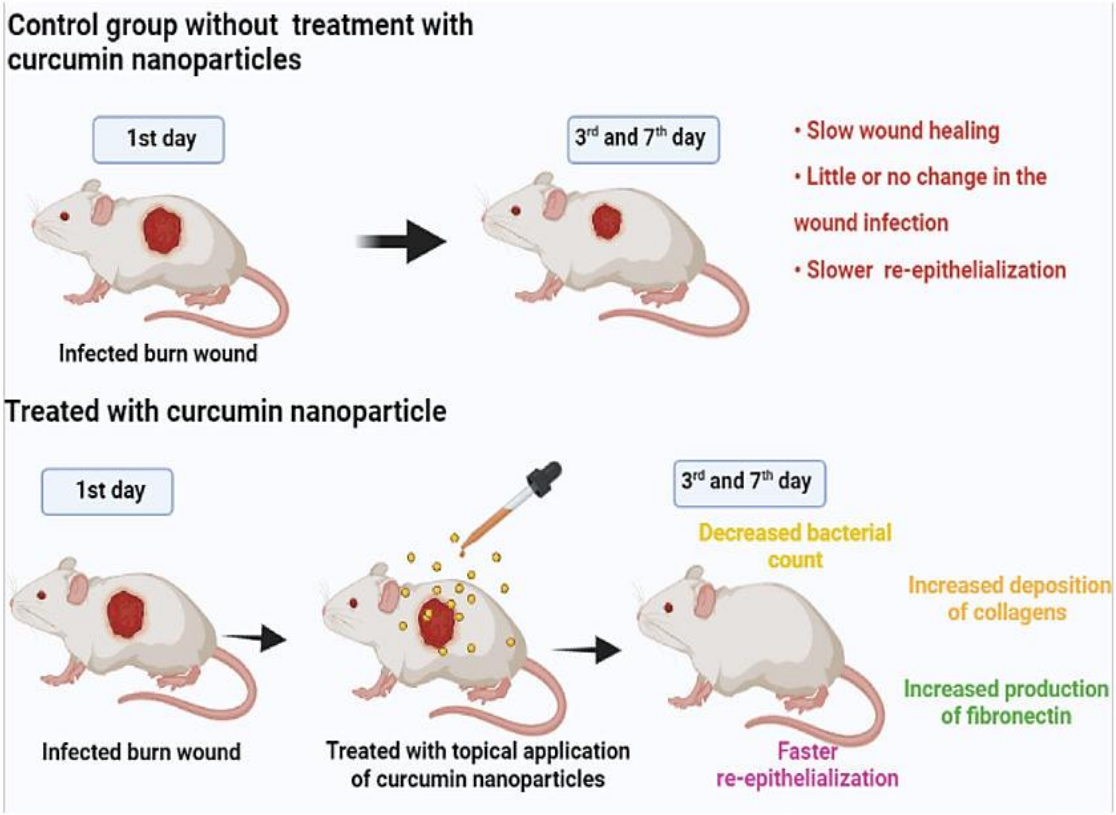

Figure 4: A schematic representation of wound healing activity of nanocurcumin study.

2.2. Hepatoprotective

According to[19], the curcumin nanoliposomes were prepared so that the size of the particle of curcumin could be reduced and also its solubility in water could be improved. As a result of this, the hydrodynamic layer surrounding the particles would be thinner with an increased rate of surface specific dissolution. It was mentioned that toxicity of the liver which includes necrosis and steatosis could be experienced as a result of any single exposure to the hepatotoxic agent CCl4. The study showed that the serum activities of alanine transaminase (ALT), Aspartate aminotransferase (AST), and alkaline phosphatase (ALP) were greatly reduced while the liver was treated with free curcumin as well as curcumin nanoliposomes. It was also noted that the treatment group receiving curcumin nanoliposomes treatment experienced lower serum activities of ALT, AST, and ALP as compared to that of the treatment group treated with free curcumin. This proved the fact that the curcumin nanoliposomes can act as the most beneficial agents for reversing any kind of injuries in the liver and exhibit the hepatoprotective effect successfully. It was also mentioned in the study that after being pre-treated with curcumin nanoliposomes followed by CCl4, the antioxidant enzymes such as catalase (CAT) superoxide dismutase (SOD) and glutathione peroxidase

(GPx) were substantially reinstated to their basal level exhibiting better efficiency of curcumin nanoliposomes against that of peroxidation of lipids. On the other hand, in Alhusaini's literature[20], nanocurcumin was used for the first time for managing the toxic effects of CuSO4 in liver tissues as it is believed that the smaller size of nanocurcumin could be especially helpful for readily interacting with the surface and inside biomolecules successfully. Maghsoumi et al. mainly carried out the study for evaluation of the protective as well as the regenerative effects of curcumin nanomicelles on the chronic liver injuries in mice which are induced by alcohol.[21] It was seen that irrespective of the little decrease in the liver enzyme levels in the group which was treated with nanocurcumin, the serum levels of AST, ALP, and ALT was reduced greatly in the post treatment groups of nanocurcumin. Thus, it was found in the study that nanocurcumin when administered at 100 mg/kg/day can be of utmost helpful in recovering the alcohol induced liver damages with bringing about a significant reduction in the lactate dehydrogenase (LDH) level. However, in this article, the clinical applications of the nanocurcumin were not conducted. In another study by[22], the hepatoprotective effect of nanocurcumin on the salinomycin induced liver toxicity in broiler chicken was studied.

2.3. Anti-Tumor

The cause of the tumor formation is often stated to be due to an imbalance amongst the cell growth and cell death, where an increase in the former and decrease in the latter is observed. This, if left untreated, leads to cancer development.[23] Hence, to treat this disease, the medical field has developed different treatment processes, chemotherapy being one of the most common treatments. According to[24], the principal for the antitumor activity of the chemotherapeutics is by triggering the apoptosis pathway, causing impairment in the microtubules and causing DNA damage of the cancer cells. However, it is being observed that the cancer cells are getting resistance to the chemotherapeutic agents, which is often called termed as "chemoresistance". The resistance of the cancer cells in induction of apoptosis is considered as one of the reasons of such phenomenon. Moreover, it is also observed that the chemo resistant cancer cells possess DNA protecting properties by stimulating DNA repairing pathways and thus preventing it from damage. Curcumin is a phytochemical which is universally considered as a potential anticancer agent, and has been proven to provide protection to all types of cancer. In a disquisition done on mouse models, it was reported that curcumin inhibited the cell proliferation as well as stimulated the apoptosis cycle. It concluded on the note of using curcumin as a potent anticancer agent.[25] Similarly,

an in vitro study found that curcumin, when administered in a dose-time dependent manner, was effective in inhibiting cancer cell growth in the lungs and increased their cell death. Along with anticancer properties, curcumin has also been proven to be effective against tumor formation by the process of autophagy. The downregulation of the PI3K/Akt/mTOR pathways results in autophagy. Moreover, the apoptosis induced by curcumin, along with the autophagy mechanism, synergistically causes toxicity for the cancer cells, leading to anti-tumor effects. The effect of nanocurcumin on breast cancer cell lines was investigated, and it was deduced that nanocurcumin was found to be an effective anti-tumor agent along with low toxicity.[26] Moreover, ref.[27] conducted a testing using a xenograft model in which it was found that nanocurcumin when used along with anticancer drugs showed a promising antiproliferative and anti-tumor effects in cancer cells which further helps in other cancer therapies. Figure 5 schematically represents the anti-tumor activity of nanocurcumin. Another advancement in nanodrug delivery is the use of nanocurmin combined with a magnetic field (NANOCUR-MF) of 8mT, which was reported to have a high anti-cancer, anti- tumor, and anti-microbial effect as in NANOCUR-MF; the solubility of nanocurmin is higher since the magnetic field helps in better membrane permeability.

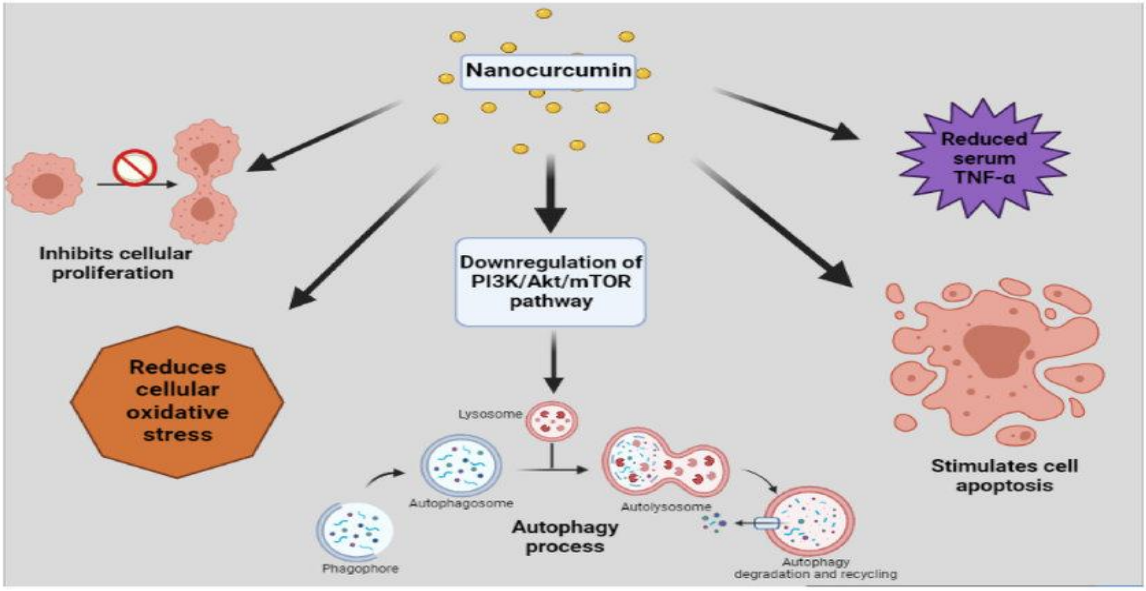

Figure 5: Schematic representation of anti-tumor activity of nanocurcumin.

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