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CURCUMIN NANOFORMULATION: A NEXT-GENERATION CURCUMIN FOR ENHANCED THERAPEUTIC POTENTIAL IN CANCER THERAPY WITH ADVANCED BIOAVAILABILITY

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ABSTRACT

Natural compounds are emerging as therapeutic agents for the treatment of cancerous diseases. The principal compound of turmeric extract, curcumin (diferuloylmethane), has attracted much attention as a plant compound with possible anti-cancer activity. Despite being administered orally in large doses, curcumin is highly nontoxic and physiologically tolerable. Low solubility, physico-chemical stability, rapid systemic clearance, and low cellular uptake restrict its use despite having potent anti-cancer activity. The creation of curcumin nanoparticle formulation to enhance its therapeutic index by improved bioavailability, localization, and cellular uptake is the central focus of this paper. This article also speaks of the limitations and challenges in formulating and delivering nano-sized curcumin particles, as well as whether using nano-formulation is feasible to deliver curcumin. One such method to enhance the delivery of drugs and drug efficacy is nanotechnology. Here, curcumin's cytotoxicity can be minimized by minimizing the dosages required for therapies using its formulating in nanoparticles. These nanoparticles can be used to deliver curcumin to targeted areas locally, preventing systemic clearance. Additionally, enhanced pharmacokinetics and cellular uptake of nano-curcumin may be achieved when using a specific coating.

KEYWORDS: cancerous diseases, therapeutic index, nano-formulation, nanoparticles, nano-curcumin.

INTRODUCTION

In industrial countries, cancer is the number one killer; in developing countries, it is the second most fatal disease. Statistics show that 7.6 million people died from cancer and 12.7 million new cases occurred in 2008.[1] Cancer can be induced by both hereditary and non-genetic factors, but the latter is more closely associated with habits such as smoking, poor diet, obesity, and lack of physical exercise.[2-4] Mutations in tumor suppressor genes, affecting fundamental cell regulatory cycles, are just one of the genetic factors that involve slow changes in genetic and epigenetic cancer-causing genes.[5,6] In addition, additional genetic changes result in aggressive growth of primary to secondary invasive cancer cells, invading surrounding healthy cells. Several early and preventive methods have been utilized to inhibit these processes as we understand more about the genetic and molecular alterations that result in cancer and its progression.[7] To stop premalignant lesions from becoming metastasized cancer cells, several possible ways are particularly formulated to stop them in their tracks.[7] According to *in-vitro* and *in-vivo* data, certain plant extracts such as curcumin, resveratrol, epigallocatechin gallate, and indole-3-carbinol possess anticancer or chemopreventive properties.[8] The active constituent of the Indian spice turmeric is curcumin, a yellow-coloured rhizome extract obtained from *Curcuma longa*, which has been extensively studied for the management of various chronic diseases. There are three major constituents of curcumin that have been characterized so far. Curcumin I (~75%), demethoxycurcumin (~20%), and bisdemethoxycurcumin (~5%) are the three principal curcumin components (Figure 1) that have been characterized so far (Figure 1). Due to its extensive range of applications, such as anti-inflammatory, anti-cancer, antidiabetic, anti-angiogenic, and antibacterial, curcumin has become increasingly popular in recent times and is referred to as a "next generation multipurpose drug".[8–12] By suppressing various intracellular transcription factors, such as NF-κB and activator protein-1, and downregulating secondary messenger expression, such as COX2, nitric oxide synthase, and matrix metalloproteinase-9, curcumin was found *in-vitro* to

cause apoptosis in a range of cancer cell lines. In addition, curcumin suppressed numerous transcription factors, inflammatory markers, and metastasis-related genes in cancer cells. Aggrawal *et al.*[13] have thoroughly reported curcumin's action on universal molecular targets, and curcumin has been shown to have different effects on signaling molecules in every type of cancer cell. Several studies have established the feasibility of using nanoformulation-based approaches to improve curcumin delivery hitherto, through liposomes, polymers, conjugates, cyclodextrins, micelles, dendrimers, and nanoparticles in *in-vitro* and *in-vivo* conditions (Ghalandarlaki *et al.*, 2014; Naksuriya *et al*., 2014; Yallapu *et al*., 2015). Of these, some curcumin nanoformulations have been the focus of intensive clinical investigation. Most researchers initially focused mainly on enhancing bioavailability, but they later shifted their focus to effective curcumin targeting in the ailing region with the assistance of aptamers, antibodies, and peptide mediation. Poly (lactic-co-glycolic acid) nanoparticles (PLGA NPs) loaded with curcumin were evaluated for oral bioavailability. Employing curcumin has the disadvantage of exhibiting limited water solubility, resulting in limited oral absorption and poor bioavailability. Despite being administered orally at high doses (i.e., 10–12 g/day), the plasma concentration of curcumin is persistently in the nanomolar range, as per a plethora of evidence.[14] Furthermore, curcumin is metabolized by the liver and intestines to form a series of metabolites, such as glucuronide and sulfate conjugates.[15] 5-50 µM doses of curcumin are required in order to produce anticancer activity, as revealed by several clinical trials.[16,17] This was confirmed through a clinical trial where patients subjected to curcumin for four months displayed no decline in tumor markers.[18] Another trial analyzed the activity of gemcitabine with curcumin at a dose of 1 g/kg/day in order to inhibit tumor activity in pancreatic cancer.[19] To enhance the poor water solubility of curcumin, various nanotechnology-based therapeutic delivery systems like nanoparticles, liposomes, and nano emulsions have been formulated.[20–24] Based on findings, these preparations minimized toxic side effects and improved treatment efficiency.[25–28] This is most likely achieved by the Nano formulated curcumin's unique localization and cell uptake within the cancer cells. With a focus on cancer therapy, this article describes the various nanotechnology approaches for curcumin delivery. Even though various nanoscale delivery systems have been developed, due to the numerous studies on these systems that have been reported in the literature, greater emphasis is placed on discussing nanoparticles, liposomes, micelles, Nano emulsions, and cyclodextrin.

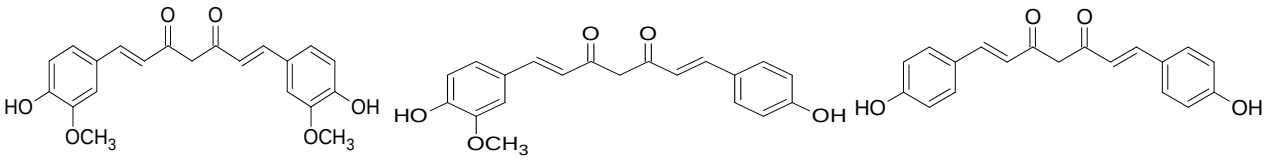

Figure 1: Major Constituents of Curcumin.

Background on history and chemical properties of curcumin: - Curcumin, chemically diferuloylmethane or 1,7-bis (4-hydroxy 3-methoxyphenyl)-1,6-heptadiene-3,5-dione, is a natural yellow pigment that is isolated from Curcuma longa rhizomes[75] While it was first discovered in 1815, its chemical structure was not explained until 1973 by Roughley and Whiting.[76] It was first isolated in 1842 as a blend of turmeric oil and resin by Vogel and Pelletier.[77] It has a molecular weight of 368.37 and is soluble in a number of organic solvents such as acetone, ethanol, and DMSO. It is badly soluble in water [78] and has a melting point ranging from 176 to 177°C. It is a unique polyphenol that has keto-enol tautomerism with keto form in acid media and an enol structure that is stable in basic solvents.[79] The compound is symmetrical with four units of chemicals consisting of aryl side chains that are connected via a methylene moiety bearing a di-keto moiety. Curcumin is a significant component of the early Chinese and Indian traditional way of life, applied either as a spice[76] or pharmaceutical agent in injury, depression, stress, infection, and dermatological diseases.[77] Multidrug resistance from existing chemotherapeutic drugs has fueled growing interest in finding and using plant-derived anticancer agents, which is the basis for the recent interest in using curcumin as an anticancer agent.[80] There is also a public perception of acceptance that plant-derived anticancer agents are safer therapy than their chemotherapeutic relatives.[81] Whether or not this is justified depends on the therapeutic data relating to the anticancer agent under consideration. Despite this, active research in the field of plant-derived anticancer agents has seen some very interesting new compounds emerging.[77]

Curcumin nanoformulations: - A plethora of curcumin nanoformulations has been developed in the last few years. Improving the solubility and bioavailability of curcumin, as well as its resistance against hydrolysis inactivation, is the central objective of the majority of attempts. Some are formulated to travel and linger inside the body for extended periods of time, while reminders have focused on intracellular release strategies and cellular delivery. Several curcumin nanoformulations have been proven to be hopeful in the detection of various human diseases and have made a vital contribution to drug applications. They are explained and discussed herein (Figure 2).

Properties of nanoparticles: - Nanoparticles possess a large contact surface area, which leads to greater bio-interactions between cancer cells and drug particles. Nanoparticles with sizes between 50-100 nm bearing minor negative and positive surface charges are readily taken up by cancer cells, and such particles generally possess little self-self and self-non-self-interactions. Since the cell membrane is negatively charged, it is also predicted that cationic nanoparticles would be effective for greater cell-nanoparticles interactions and subsequent increased cellular uptake of particles.

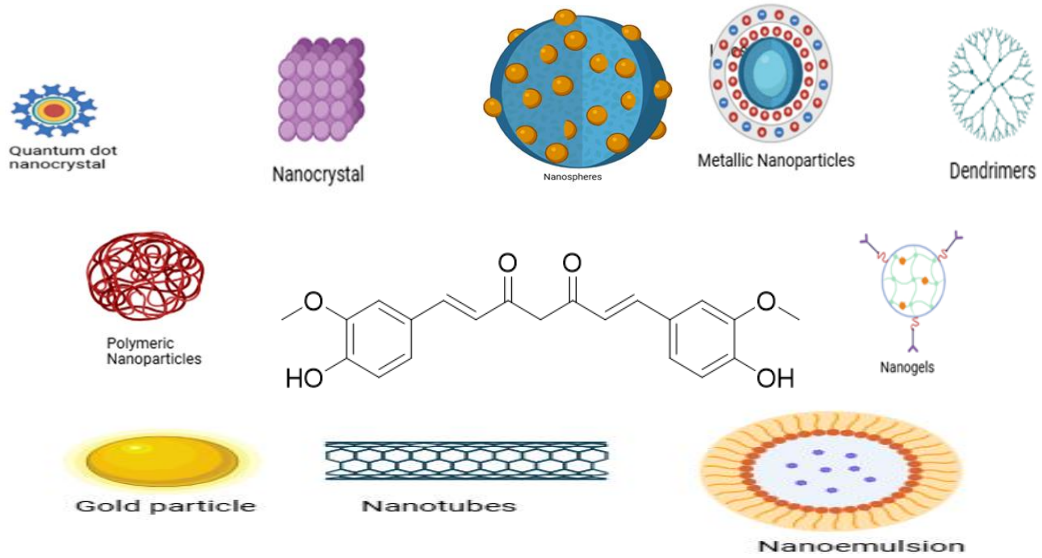

Figure 2: Curcumin nano particles.

Polymeric encapsulated curcumin Nanoparticles: - It is widely believed that the diameter of a nanoparticle must be between 10 and 100 nm to be effective as a cancer therapy. The glomerular capillary wall sieving coefficient, which is the premise that the kidney rapidly eliminates any nanoparticles less than 10 nm in size, is the rationale for the lower cut-off diameter.[29] In addition, most cancers have vascular cut-off hole diameters ranging from 380 to 780 nm, while normal vascular cells will only allow particles less than 2 nm in size.[30] Tumor cells may be easily permeated by nanoparticles of an outer positive charge and of 100 to 150 nm in size.[31] One of the most promising approaches to enhance curcumin's bioavailability and reduce its rate of degradation in vivo is to nano encapsulate it with polymers. Curcumin nanoencapsulation has been achieved thus far with various synthetic and natural biodegradable polymers, including silk fibroin, chitosan, N-isopropylacrylamide (NIPAAM), N-vinyl-2-pyrrolidone, polyethylene glycol monoacrylate (NIPAAM [VP/PEG A]), poly (vinyl alcohol) (PVA), and poly (lactic-co-glycolic acid) (PLGA).[20,21,32]These polymers are typically characterized by biocompatibility, biodegradability, easily controllable physicochemical properties, and the ability to provide the drug with a controlled release. Encapsulation of curcumin nanoparticles with PVA and PLGA enhanced the killing effect against cancer cells, as reported in a recent study by Mohanty and Sahoo.[21] PLGA-encapsulated curcumin nanoparticles were proved in different research studies to be responsible for promoting cellular uptake within various cancer cell lines. [20,32–34] Size dependency and entrainment efficiency as a function of lactide:glycolide ratio were established through the manufacturing of PLGA-encapsulated curcumin nanoparticles.[20] The smallest and most active curcumin nanoparticles were the ones bearing 50:50 ratios. Besides, compared to 75:25 curcumin nanoparticles and native curcumin (not synthesized as nanoparticles), the 50:50 curcumin nanoparticles were the most cytotoxic to human epithelial carcinoma cells (HeLa).[20] At the same time, curcumin nanoparticles encapsulated in PLGA were also capable of inhibiting the proliferation of cisplatin-resistant ovarian cancer cells, aside from sensitizing the cells to radiation and chemotherapy treatments.[35] By employing PVA and poly(L-lysine) as stabilizers during the preparation of nanoparticles, the scientists significantly enhanced the antiproliferation activity of curcumin nanoparticles against ovarian (A2780CP) and breast cancer cells (MDA-MB-231). Nanoparticles with a unimodal size distribution and higher form homogeneity were prepared by incorporating these stabilizers. In addition, curcumin nanoparticles were prepared with a controllable size distribution ranging from 76.2 to 560.4 nm. Consequently, the research established that both tested cancer cell lines possessed significantly higher cellular uptake, thus generating stronger curcumin nanoparticle antiproliferation activity.[33] Anti-P-glycoprotein (P-gp) conjugation of PLGA-encapsulated curcumin nanoparticles boosted their cytotoxicity against multidrug-resistant cervical carcinoma.[34] Curcumin has also been encapsulated in copolymers such as NIPAAM, N-vinyl-2-pyrrolidone, and polyethylene glycol monoacrylate (NIPAAM

[VP/PEG A]). The obtained nanoparticles were relatively mono disperse with an average particle size of 50 nm and permeable to various types of pancreatic cancer cells.[36] It was shown that curcumin nanoparticles with NIPAAM (VP/PEG A) coating were highly effective in controlling the vitality of glioblastoma and medulloblastoma cells. Curcumin has been found to suppress the IGF pathway, which is vital for the growth and dissemination of brain cancers[37], according to initial findings. Since it is nontoxic, nonimmunogenic, and easily tolerated in vivo, human serum albumin is an ideal drug carrier that does not require stabilization using surfactants or other polymers. Furthermore, drug nanoparticles with albumin coating usually degrade into small complexes (10 nm) that fail to clog capillaries.[38] This approach synthesized curcumin nanoparticles with high loading capability and low tissue irritability and toxicity.[39] The results of Bourassa et al.[40] showed that the entrapment of curcumin within particle matrices is significantly improved by the availability of multiple sites for drug binding on albumin molecules. Albumin encapsulation also enhanced drug nanoparticle endocytic uptake and drug deposition in tumor sites, enhancing passive drug targeting to tumors.[41] Kim et al. recently demonstrated that curcumin nanoparticles bound to albumin increased the in vitro cytotoxicity of curcumin against pancreatic cancer (MiaPaCa2) and colon cancer (HCT 116).[42] The effect of surface-charged nanoparticles on cytotoxicity against cancer cells has been the focus of many studies.[43, 44] From flow cytometry results, curcumin nanoparticles encapsulated in chitosan-PCL also rapidly internalized into the Hela cervical cancer cell line.[45] To deliver curcumin for cancer treatment, a carboxymethyl-chitosan nanocarrier with a negative charge and 150 nm of mean particle size was also fabricated. When 5 mg/ml of carboxymethyl-chitosan curcumin nanoparticles were supplemented into the media, the in vitro viabilities of PC-3 and MCF-7 cells were reduced to 30%, but these cancer cells also exhibited a greater rate of apoptosis.[44]

Liposomal curcumin nanoparticles: - Since liposomes contain both hydrophobic and hydrophilic groups within their structure, they are an interesting drug delivery vehicle. Most of the molecules present in the hydrophobic layer are cholesterol and phospholipids. Water-insoluble chemopreventive drugs such as curcumin, resveratrol, oryzanol, and N acetyl cysteine can be delivered through this lipid-based carrier. The drug can be located within the phospholipid bilayer, bilayer water interface, or internal space of liposomes, based on its lipophilicity. The rate of drug release, permeability, cellular uptake, targeting, and biodistribution are all individually controlled by liposomes.[46] Compared to dipalmitoylphosphatidylcholine (DPPC) and egg phosphatidylcholine (PC) additives, application of dimyristoylphosphatidylcholine (DMPC) in liposome-based curcumin nanoparticle preparation has resulted in a greater encapsulation of curcumin and tunable particles ranging from 100 to 150 nm.[47] Moreover, 70–80% of cellular activity of human prostate LNCaP and C4-2B cancer cells was suppressed by DMPC-based loaded curcumin liposomes. As a significantly ten-fold greater amount of raw curcumin was needed to induce an analogous cellular response, the loaded curcumin liposomes were definitely more efficient than raw curcumin in killing prostate cancer cells.[47] The higher uptake of liposomes into living cells compared to other curcumin nanoparticles is another widespread factor that could trigger the killing ability of liposomal curcumin in cancer cells. Greater curcumin has been shown to be delivered to cells through liposome-based carriers compared to albumin or free curcumin. Additionally, it has been found that lymphoma cells (EL4) possess a relatively greater uptake of liposomal curcumin compared to lymphocytes.[48] Apolipoproteins were utilized successfully as a stabilizer to form a novel phospholipid-curcumin nano-disk with a diameter of <50 nm and a thickness of the phospholipid bilayer. In comparison with raw curcumin, these nano-disks of curcumin showed a higher antiproliferative activity against hepatoma and Jeko lymphoma cells. In addition to this, these nano-disks induced cancer cells to undergo increased apoptosis.[49] Liposome-based formulations of curcumin have displayed strong anticancer activity. [50–52] Li et al. discovered that even though NF-κB, COX-2, and IL-8 expressions were all simultaneously down-regulated, the effectiveness of liposomal curcumin on six different human pancreatic cancer cell lines was comparable with or superior to that of dissolved raw curcumin.[50] In another study, liposomal curcumin significantly inhibited NF-κB expression in the CAL27 and UM SCC1 head and neck cancer cell lines. [51] Cationic polyethylene glycol (PEG) and polyethyleneimine (PEI) complexes have been employed to prepare positively charged curcumin-encapsulated liposome nanoparticles (REF). The cytotoxicity activity against numerous cancer cell lines, such as human cancer cells (HepG2 hepatocellular carcinoma, A549 lung carcinoma, HT-29 colorectal adenocarcinoma, and cervical carcinoma) and murine cancer cells (B16F10 melanoma, LL2 lung carcinoma, CT26 colorectal adenocarcinoma, and JC breast adenocarcinoma), were approximately 20 times higher than that of raw curcumin.[52] This was irrespective of the low encapsulation efficiency of the method of 45%. When this formulation was given in vivo to mice with CT26 and B16F19 cells, the growth of tumor was strongly inhibited by 60–90%.[52] Ruby et al. also demonstrated anticancer activity in mice using neutral liposomes.[53] Another formulation engineering approach to cancer therapy is encapsulating curcumin with co-anticancer drugs. This is achieved since the combined effects of various drugs might intensify anticancer effects and reduce cytotoxicity to nonmalignant cells.[54] Compared to oxaliplatin alone, combinations of liposome-based curcumin and oxaliplatin also produced an enhanced inhibition of human colorectal cancer growth. [55] A fascinating approach was taken by Narayanan et al. to inhibit prostate cancer, namely in association with cell

proliferation, apoptosis, cell cycle and cyclin D1, m-TOR, and activation of p-Akt. They achieved this through the use of two natural phytochemical molecules (curcumin and resveratrol) together with liposomes as a vehicle of delivery.[56]

Micelles curcumin nanoparticles: - A macromolecular aggregate of block amphiphilic copolymers in water solutions, a polymeric micelle (PM) is formed when hydrophobic interactions with water-insoluble pieces lead to the development of a spherical core and inner shell.[57] Micelles and liposomes are not identical. Liposomes are built of lipid monolayers, whereas micelles are composed of lipid bilayers. Application of PM as a drug delivery system for hydrophobic drugs has various advantages, including enhanced tissue penetration, extended circulation time, reduced toxicity to normal cells, and enhanced drug stability and solubility. The synthesis of PM entails the application of a number of biocompatible and biodegradable amphiphilic block copolymers, including pluronic, poly (ethylene glycol)-b-poly (D, L-lactide) (PEG-PDLLA), poly (ethylene glycol)-b-PCL (PEG-PCL), and poly (ethylene glycol)-b-poly (lactide-co-glycolic acid) (PEG-PLGA) and others. Pluronic is the most common polymer for micelle systems and relies on hydrophobic/hydrophilic interactions for micellization. It consists of hydrophobic and hydrophilic block copolymers of poly (ethylene oxide) PEO and poly (propylene oxide) PPO, respectively. For example, Sahu et al. illustrated that even though the rate of release of curcumin was the reverse, higher molecular weight Pluronic (F127) was more effective in curcumin entrapment compared to the lower molecular weight Pluronic (F68). After 10 days, F68-encapsulated Pluronic nanoparticles released more than 80% of their curcumin content, whereas nanoparticles encapsulated by F127 released 60%. The in vitro cytotoxic effect on HeLa cells was also affected by this; IC50 values for free curcumin, pluronic F68, and pluronic F127 were 14.32, 16.01, and 17.45 µM, respectively.[58] Synergistic behaviors, such as improved micelle stability, drug loading capacity, increased residence time, better cytotoxicity effect on cancer cells, and reduced reticuloendothelial systems (RES) entrapment, were evidenced by the mixed micelles formulated with two pluronic copolymers of different hydrophilicity.[57,61] For example, through maintaining the micelles in a dispersed state, pluronic F68, of a relatively higher hydrophilic ethylene oxide (EO) block, stabilized the self-assembly of pluronic F123. Hydrophobic curcumin molecules were incorporated into pluronic F123 since it contains more hydrophobic sites.[62] There have been several studies on the delivery of curcumin to cancer cells through micelle systems based on polymeric materials. To deliver curcumin to human prostate cancer cell line, PC-3, Song et al. used nanosized polymeric micelles (~30 nm, PDI of < 0.15), which were synthesized from amphiphilic methoxy poly (ethylene glycol)-b-poly (e-caprolactone-co-p dioxanone) (MPEG-P[CL-co-PDO]).[59] In contrast to raw curcumin, the mixed micelle copolymers demonstrated a comparable dose-dependent cytotoxic effect on cancer cells, long-term drug release profile, and high encapsulation efficiency (> 95%). Furthermore, the uncharged micelle carrier was free from any negative effects.[59] Yet in another study, HeLa cells were compared against four different micelle systems comprised of PEG and aromatic acids. The researchers found that aside from the fantastic anticancer efficacy, there was minimal acidification of the micelles since the solution pH wasn't altered remarkably (it only stayed between 6.9 and 7.0). This finding suggested that damage caused by the acidity of adjacent tissues may be avoided in vivo.[60] In a recent application, methoxypoly (ethylene glycol) (mPEG) and palmitic acid were employed as hydrophilic and hydrophobic blocks to design a novel nano-micelle carrier for HeLa cell therapy. Since the esterase enzyme, or lipases, exist in human beings and can lead to the release of the drug encapsulated, fatty acid drug carriers are favored. This approach yielded relatively small micelle particles (41.4 nm) and perhaps very high curcumin encapsulation efficiency (nearly 100%). Intestinal fluid (pH 6.8), stomach fluid (pH 1.2), and physiological fluid (pH 7.4) were all found to be stable in this micelle system.[63] Esmaili's group recently fabricated casein micelles from camel milk and their report on the enhanced solubility, anticancer, and antioxidant activities of curcumin-loaded micelles was consistent with previously published findings.[64] Amphiphilic self-assembly protein beta casein shares resemblance to block copolymer micelle aggregates. Based on qualitative microscopic observations and results from an MTT assay, Sahu et al. concluded that curcumin-loaded bovine micelles with a diameter of less than 200 nm were slightly more toxic to cancer cells compared to raw curcumin.[65]

Nano-emulsion: - Nano-emulsions are emulsions with nanoscale dimensions and are employed to enhance the delivery of active medicaments. These are thermodynamically stable isotopic systems where an emulsifying agent, i.e., surfactant and co-surfactant, is employed to mix two immiscible liquids into one phase. Nano-emulsion droplets are usually 20–200 nm in diameter. Curcumin-loaded nano-emulsion facilitates more efficient, systematic, and convenient curcumin application procedures. Pharmacological activities of curcumin, such as cancer treatment, inflammation, and antioxidant activity which nano-emulsion formulation increases the respective activity. Curcumin nano-emulsion formulations have been researched thoroughly, with curcumin being loaded into nano-emulsion for topical application to cure psoriasis.[157] In psoriatic mice, these curcumin nanogels show quicker and earlier healing compared to curcumin.[155] Curcumin nano emulsions were useful in hepatic and cardiac disorders as well as in testicular defects.[156]

Development of curcumin nanogels: - While the application of hydrogels and nanogels for drug delivery is not novel, there is still relatively little work on the delivery of curcumin into cancer cells and the subsequent biological interactions. Besides the properties of other nanosized vesicles,[66,67] nanogels, being the nanoscale counterpart of hydrogels (which are restricted to nanoscale), possess properties similar to their macro-counterparts, including high stability in water, high water content, and swelling ratio. Other unique features of nanogels are their enormous total surface area and porous nature, which are beneficial for drug conjugation and storage, respectively.[67,68] A biocompatible and biodegradable curcumin-containing chitin nanogel was developed by Mangalathillam's group in 2012 and delivered transdermally for treating skin cancer.[67] Pulmonary delivery of curcumin hydrogel microspheres was first developed recently, and it showed promising aerosolization behavior. In an in vitro cytotoxicity experiment, 800 µg/ml of PLGA-curcumin loaded with chitosan-grafted-PEG was incorporated, and it led to more than 50% inhibition in cell viability.[69] In another study, curcumin was encapsulated in alginate-chitosan-pluronic nanogels prepared via a polycationic cross-linking method. The nanogels were further tested for their efficacy to treat cancer in vitro. The cytotoxicity effect of encapsulated curcumin against HeLa cells was not statistically better than that of unprocessed curcumin, even though there was greater encapsulation efficiency (approximately five to ten times).[70]

Cyclodextrin-curcumin complexes: -Curcumin complexation with cyclodextrins for the treatment of cancer has been investigated in a limited manner. [26,71,72] The cyclic oligosaccharides, cyclodextrins, contain a lipophilic interior and hydrophilic exterior.[71] Hydrophobic drugs, including curcumin, may subsequently complex and be incorporated into the central cyclodextrin core. Enhanced stability, bioavailability, minimized curcumin degradation, and avoidance of nonselective toxicity against nonmalignant cells are all advantages of cyclodextrin.[71] Tested against a range of cancer cell lines, including KBM-5 (human chronic myeloid leukemia), SSC-4 (human head and neck squamous cancer), Caco-2 (human colonic carcinoma), and Panc-28 (pancreatic cancer), a cyclodextrin-curcumin self-assembly complex was statistically more cytotoxic than crude curcumin. The researchers of another study developed self-assembly poly(b-cyclodextrin) curcumin (PCD30), which had a significantly greater anticancer effect compared to their previous formulation of cyclodextrin curcumin. Poly (ADP ribose) polymerase (PARP) protein cleavage was prominent in PCD30-treated cells, reflecting apoptosis-mediated cell death.[72]

Other curcumin nanoformulations: - Another efficient method of delivering curcumin is through the nano emulsion technology since this polyphenol molecule is lipophilic. Curcumin delivery through nanoemulsion formulation has been reported only in a few studies.[24,73,74] With tween 80 as a surfactant, a curcumin lipid nano emulsion with a mean particle size of 47–55 nm was developed. Nevertheless, compared to free curcumin, these curcumin nano emulsions were less active against a range of leukemic cell lines such as promyelocytic leukemia (HL60), chronic myeloctic leukemia (K562), lymphoblastic leukemia (Molt4), and monocytic leukemia (U937). This may be attributed to the poor availability of curcumin since the release rate was too low.[73] As compared to raw curcumin, curcumin nanoemulsion exhibited decreased toxicity against oral squamous cancer cells (OSCC-4 and OSCC-25) in another independent study. Curcumin creams are often formulated through solid lipid technology since it enhances the stability of curcumin under no sun exposure. Solid lipid technology for curcumin administration in cancer therapy has not experienced significant development. It was also found that transferrin-mediated curcumin solid lipid nanoparticles were able to restrict the growth of MCF-7 breast cancer cells. Curcumin-loaded solid lipid nanoparticles and cells treated with an equivalent dose of 3 µM raw curcumin possessed respective viabilities of 80 and 67%. Only 42% of cells survived in the presence of transferrin. In addition, when compared to raw curcumin (30%) and curcumin solid lipid nanoparticles (60%) curcumin-mediated curcumin exhibited a higher rate of apoptosis (90%).[74]

Curcumin Gold Nanoparticles: - Gold nanoparticles are primarily applied in cancer diagnosis but can be potential drug carriers owing to inherent surface chemistry and multi-functionalization potential, surface plasmon resonance, stability, and formulation ease. In addition, they are non-toxic, non-immunogenic, highly retentive, and highly permeable, which ensure good bioavailability of drug cargoes in tumors.[82] Curcumin-loaded chitosan-graftpoly (N-vinyl caprolactam) gold nanoparticles prepared by ionic cross-linking and administered to CT26 xenografted Swiss albino mice was detected in circulation after 7 days with no toxicity detected. Most importantly, a considerable amount of curcumin (3 µg/g) was targeted at the CRC tumor sites. Additionally, the nanoparticles persisted in the CRC tumor for 2 weeks, which confirms its high retention property.[83] Gold nanoparticles may induce host immunological stimulation, thus preventing them from being used as a drug carrier.[84]

Anticancer activities of curcumin: - A disruption in the normal balance between cell division and cell death is one of the primary causes of cancer. Two main pathways can induce apoptosis signals: the intrinsic route and the extrinsic route. The intrinsic pathway prevents the synthesis of the anti-apoptotic proteins Bcl-2 and Bcl-xL by activating the mitochondrial membrane. Curcumin modulates the cancer cells' mitochondrial membrane potential by suppressing the Bcl-xL protein. The extrinsic apoptotic cascade induces cell death via the

upregulation of death receptors and induces apoptosis in response to tumor necrosis factor alpha (TNF-α). Curcumin and its derivatives also have a potent ability to induce apoptosis in a variety of cell lines via the suppression of intracellular transcription factors, such as nitric oxide synthase, signal transducer and activator transcription 3 (STAT3), and matrix metalloproteinase-9 (MMP-9). Moreover, curcumin prevents glucose uptake and lactate production in cancer cells by inhibiting pyruvate kinase M2 through downregulation of the mammalian target of rapamycin (mTOR)-hypoxia-inducible factor 1.

Curcumin Effect against different cancer: - Curcumin has been effective in the growth and proliferation inhibition of cancer cells in several cancers such as gastrointestinal, head and neck, brain, pancreatic, colorectal, breast, and prostate cancers. Its efficacy has been evaluated in animal models and human cell cultures in several studies (Figure 3).

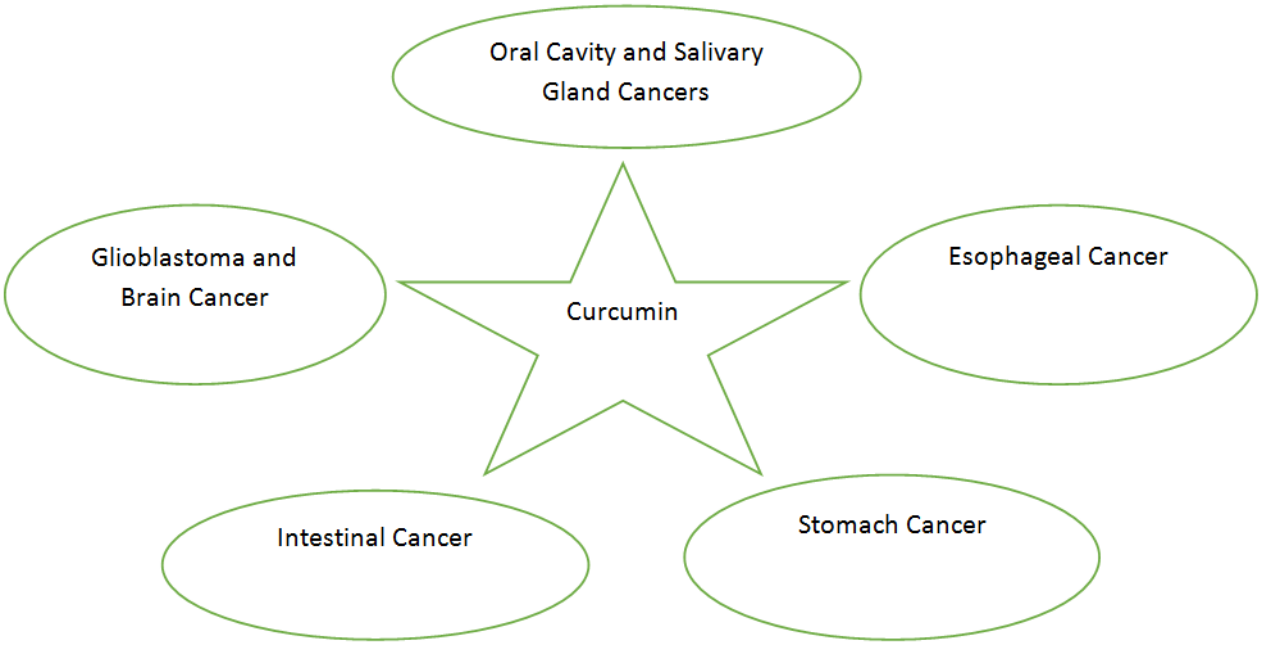

Figure 3: Curcumin is Effective Against Different Type of Cancer.

Oral Cavity and Salivary Gland Cancers: - Though there are limited studies on the activities of curcumin in oral cavity cancers, curcumin has revealed promising activities in oral carcinogenesis prevention. Curcumin per se[89,90] or in association with piperine[91] significantly suppressed oral carcinoma formation in the 7, 12-dimethylbenz[a] anthracene hamster buccal pouch model of carcinogenesis, which may be attributed to the antioxidant as well as anti-lipid peroxidative activities of the curcumin and its carcinogen detoxification modulation activity. Curcumin has been found to exert anticancer effects through the enhancement of systemic as well as local anti-oxidant status, thus preventing DNA damage as well as lipid peroxidation.[92] Curcumin has also been found to be an oral cavity chemopreventive agent because of its capacity to suppress the carcinogen activation by the induction of expressions as well as activities of cytochrome P-450 (CYP) 1A1 and/or CYP1B.[93] Curcumin treatment suppressed the growth inhibition of in vitro cell by modulating the translation machinery kbmucosa epithelial cells (NOM9-CT) was not suppressed.[94] Curcumin lowered the expression of heat shock protein 70 (HSP70) in oral epithelial GNM cells. HSP70 protein levels have been found to be correlated with tumor progression.[95] Chang et al.[96] showed in a study that curcumin stimulates p38 in oral keratinocytes, which can further activate the trans activator of CCAAT/enhancer-binding protein alpha to induce insulin-like growth factor binding protein-5 (IGFBP-5). IGFBP-5 upregulation has been associated with preventing oral cancer cell tumorigenesis in xenografts of mouse models. Curcumin exhibited anti-motility activity, which was enacted by inhibiting MAPK/ERK and NF-κB pathways and thereby proteolytic enzyme downregulation like matrix metalloproteinases (MMP)-2/9 and urokinase-type plasminogen activator (uPA) in the invasive oral squamous carcinoma cell line YD-10B. In addition, curcumin-withdrawn smokeless tobacco facilitated COX-2 mediate expression and NF-κB activation in oral cancer and premalignant cells in vitro. Curcumin induced apoptosis through generation of reactive oxygen species (ROS), which shows that curcumin may induce cell death in these cancer cells.

Esophageal Cancer: - Squamous cell carcinoma and adenocarcinoma are the two most common esophageal cancers. However, the survival rate of esophageal cancer patients is still low using the current therapeutic drugs. Therefore, effective and new therapeutic strategies to

esophageal cancer should be developed, but very few studies have explored whether curcumin can be a potential candidate. Curcumin suppressed NF-κB activity and caused apoptosis in OE33 and Flo-1 adenocarcinoma cell lines. In addition, curcumin increased cisplatin and 5-fluorouracil-induced chemosensitivity.[97] Curcumin triggered cell death in two adenocarcinoma cell lines including OE19 and OE33 and two squamous cell carcinoma cell lines including KYSE450 and OE21 in a dose-dependent manner, perhaps by suppressing the ubiquitin-proteasome system.[98] Curcumin antagonized the esophageal squamous cell carcinoma growth-associated mitogenic activity of prostaglandin E2 (PGE2) in the squamous cell carcinoma cell line HKESC-1.[99] Besides its potent chemotherapeutic effect, curcumin may have chemopreventive action in esophageal cancer. Curcumin suppressed the multiplicity and incidence of preneoplastic lesions when given during initiation and post-initiation phases in N-nitrosomethylbenzylamine-induced rat model of esophageal carcinogenesis.[100]

Stomach Cancer: - Esophageal Cancer Infection of gastric epithelial cells by Helicobacter pylori is an important mechanism in the development of gastric cancer. In fact, among the proposed molecular processes among H. pylori-mediated carcinogenesis is aberrant expression of activation-mediated cytidinedeaminase (AID), which is a pathway involving activation of NF-κB by H. pylori.[101] Curcumin suppressed the downregulation of H. pylori-mediated AID expression through suppression of NF-κB pathways.[102] Curcumin additionally possessed in vitro and in vivo antimicrobial activity against H. pylori and killed H. pylori.[103,104] Thus, curcumin can be considered to be a potent chemopreventive agent for H. pylori-induced gastric carcinogenesis.[102-105] Another mechanism that has been implicated in the process of chemoresistance Squamous cell and adenocarcinoma are the two foremost forms of cancer of the esophagus. However, the survival rate for patients suffering from esophageal cancer continues to be poor using current therapeutic modalities. Thus, there is a need for novel and efficient therapeutic strategies for esophageal cancer, but few studies have assessed whether curcumin can be a candidate. Curcumin inhibited NF-κB activity and induced apoptosis in OE33 and Flo-1 adenocarcinoma cell lines. In addition, curcumin potentiated cisplatin and 5-fluorouracil-induced chemosensitivity.[97] In a dose-dependent manner, curcumin activated cell death in two adenocarcinoma cell lines such as OE19 and OE33, and two squamous cell carcinoma cell lines such as KYSE450 and OE21, perhaps through inhibition of the ubiquitin-proteasome system.[98] Curcumin partially reversed esophageal squamous cell carcinoma growth-associated mitogenic activity of prostaglandin E2 (PGE2) in the squamous cell carcinoma cell line HKESC-1.[99] In addition to its potent chemotherapeutic activity, curcumin could have chemopreventive activities against esophageal cancer. Curcumin inhibited the multiplicity and incidence of preneoplastic lesions when administered during initiation and tumorigenesisincludesRho, NF-κB, and Rhoeffectorsrhotekin(RTKN).[106] Curcumin inhibited the RTKN-induced anti-apoptotic effect in AGS cells [106] which is a cell line that was previously used to demonstrate that curcumin is able to inhibit the growth of gastric carcinoma cells.[107] Curcumin inhibited proliferation and invasion through down regulation of the activity of p21-activated kinase 1 (PAK1) and cyclin D1 expression in cultured gastric cancer cells (MGC803, MKN1, SGC7901, and BGC823.[108] In addition, reduced cyclin D and E levels were noted after induction of apoptosis through curcumin in KATO-III gastric cancer cells.

Intestinal Cancer: - Anti-tumor activity of curcumin has been most clearly explained in intestinal cancers using in vivo animal models and cultured tumor cells. Curcumin was better tolerated and pharmacologically active concentrations can be achieved in colorectal tissues in humans after oral administration. Yet more intensive studies are needed on the anti-tumor effects of curcumin in patients.[109-112] Chemopreventive effects of curcumin have been established in tumor xenografts and in transgenic mice. Curcumin reduced the inhibited tumor growth[113-117] or number of abnormal crypt foci[117,118] in the Azoxymethane[114–117,119] and the 1,2-dimethylhydrazine-stimulated[113,118] rat colon cancer model. Furthermore, curcumin treatment suppressed tumor growth in HCT-116 colon tumor-bearing mouse models.[120] Several curcumin analogs were more effective than curcumin in certain tumor models; for instance, GO-Y030 was more active than curcumin in inducing apoptosis in cultured human colorectal cancer cells[121] and increased the lifespan in Apc (580D+) mouse models.[121,122] EF24 significantly suppressed the growth of HCT-116 colon cancer xenografts.

Head and Neck Cancer: - Worldwide, head and neck squamous cell carcinoma (HNSCC) is regarded as the sixth most prevalent type of cancer, and annually, more than 30,000 HNSCC cases are identified. Overall, HNSCC occurs in the oral cavity, larynx, pharynx, and paranasal cavities. In vitro studies in different head and neck cell lines have established it. Cancer which curcumin can inhibit cell growth due to its effects on multiple cellular pathways involved in cell growth (particularly STAT3 and NF-κB), which have been found to be overexpressed in many head and neck cancers. In addition, curcumin is also capable of NF-κB downregulation and inhibition of the interleukin-6 (IL-6)-induced STAT3 phosphorylation, which can ultimately lead to the inhibition of cancer cell proliferation.[88] In one study, Kim et al.[88] quantified curcumin's activity towards inhibition of proin flammatory cytokines and I κB kinase Beta (IκKβ) activity in HNSCC patients. These patients were given chewable tablets of curcumin (2 mg), then patient saliva samples were taken before and after giving chewable curcumin tablets. There was

minimal reduction in the expression of IL-8 in eight out of 21 samples post-curcumin. There was also a significant reduction in the expression of several other cytokines, such as IL-2, IL-12p70, IFN-γ, and IL-10 grouped together, as well as tumor necrosis factor alpha (TNF-α) and granulocyte-macrophage colony-stimulating factor grouped together.

Glioblastoma and Brain Cancer: - In humans, glioblastoma (GBM) is the most prevalent form of malignant brain tumor and is accountable for approximately 15% of all CNS tumors.[123,124] Radiation therapy and surgery to treat GBM and brain tumors are limited because of cancer cell invasion into the normal brain, which will subsequently have harmful effects even after treatment.[125] Accordingly, interest in alternative treatments using naturally derived substances like curcumin is increasingly on the rise owing to their low side effects as compared to traditional treatments. Curcumin has the ability to act upon numerous molecular targets, thus combating the brain tumors that may require more than one cellular process, such as metastasis, invasion, angiogenesis, autophagy, and apoptosis. Blood–brain barrier (BBB) penetration is considered the rate-limiting step for many anti-cancer drugs, but curcumin demonstrated the ability to penetrate BBB at higher concentrations.[126] It has been demonstrated by an in vivo study (human glioma U-87 cells xenografted into athymic mouse models) that curcumin possesses the ability to suppress glioma angiogenesis through downregulation of endothelial cell markers (i.e., CD105 and CD31 mRNA) and inhibition of MMP-9.[126] In curcumin-induced G2/M cell cycle arrest in U-251 malignant glioblastoma cells, elevation of protein kinase 1 (DAPK1) level was revealed to explain this event, implying inhibition of DAPK1 by curcumin induces cell arrest and in addition triggers suppression of NF-κB and STAT3 as well as caspase-3 activation.[127]

Breast Cancer: -Breast cancer is one of the leading causes of female mortality. [86] It has been found from the meta-analysis of 21 retrospective studies that even after endocrine therapy, chemotherapy, radiotherapy, and lumpectomy, the incidence rate of breast cancer remains high.[128] Therefore, effective therapeutic strategies are required. In MCF-7 breast cancer cells and MCF-10A human mammary epithelial cells[86] a very good decrease in telomerase activity was observed as a result of curcumin treatment in a dose-dependent fashion, which was shown to be related to hTERT downregulation through curcumin rather than the c-Myc mRNA pathway. [86] In BT-483 and MDA-MB-231 breast cancer cell lines, curcumin's activity on NF-κB, matrix metalloproteinases, and cell-cycle regulatory proteins was also evaluated. Curcumin has been found to downregulate NF-κB, which in turn can lead to antiproliferative activity. However, decreased CDK4 BT-483 and cyclic D1 in the MDA-MB-231 cells was also observed with the treatment of curcumin. Curcumin and arabinogalactan combined treatment caused apoptosis by disrupting the mitochondrial membrane, increasing ROS levels, and decreasing glutathione in the MDA-MB-231 cell line. In addition, curcumin also inhibited breast tumors by overexpression of the p53 gene and through reducing the antigen ki-67 levels. In another study, also inhibited the levels of inflammatory cytokines CXCL1/2 in MDA-MB-231 cells. Additionally, inhibition of CXCL1/2 by curcumin also inhibited the expression of several metastasis-inducing genes such as chemotactic receptor CXCR4. It was also indicated that through the inhibition of different kinds of steroid receptors, dimethyl curcumin (ASC-J9) is potent against estrogen-reliant breast cancer.[86]

Colorectal Cancer: - Colorectal cancer is a highly prevalent type of malignant cancer. Besides chemotherapy, tumor tissue was also removed from the patients with colorectal carcinoma surgically, but more than half of the patient's experienced relapses.[129] Curcumin treatment decreased the amount of M1G in malignant colorectal cells without changing the amount of COX-2 protein. Also, administration of down-regulated the miR-21 gene (which is overexpressed in colorectal cancer cells) through inhibiting the binding of activator protein 1 (AP-1) with miR-21 promoter.[130] Curcumin treatment in HCT116 colorectal cancer cells induced cell cycle arrest at the G2/M phase through miR-21 gene regulation and inhibited the growth of tumor tissues.[130] It has been established that better response to radiation therapy can be achieved by incorporating curcumin in the therapy since curcumin is capable of targeting NF-κB. In another study, the inhibitory action of curcumin was augmented against colon cancer cells by mixing curcumin with ERRP (pan-ERBB inhibitor). [131] Sharma et al.[87] in a dose-escalation trial assessed the pharmacological activity of curcumin in 15 patients with advanced adenocarcinoma of the colon or rectum that was resistant to conventional chemotherapies. For a maximum of four months, study participants were given different doses of oral curcumin from 0.45 to 3.6 g/day. Subsequently, curcumin and its metabolites were also measured in plasma, feces, and urine. In addition, levels of oxidative DNA adduct (M1G), glutathione S-transferase (GST) activity, and the degree of ex vivo stimulation of PGE2 in patient blood leukocytes were assessed as biomarkers of curcumin activity. Intact curcumin and glucuronide and sulfate conjugates of curcumin have also been found to be detected in plasma at a level of 10 nmol/L and even in urine.[87] Indeed, no dose-limiting toxicities were observed. Notably, neither was there any activity upon basal PGE2 levels within leukocytes seen after curcumin treatment with any of the doses, nor was there any changes observed within the LPS-induced PGE2 production with doses between 0.45 and 1.8 g/day.

Prostate Cancer: -From an American Cancer Society recent report, approximately 2.9 million men have received a diagnosis of prostate cancer in the United States,[132] which renders the cancer the second primary

source of cancer-related death among men.[133] Curcumin has demonstrated a strong ability to induce apoptosis and inhibit proliferation in prostate cancer both in vivo and in vitro[134] by modulating multiple cellular mediators such as NF-κB, EGFR, and MAPK. [135,136] Curcumin was found in a study to have the ability to induce protein kinase D1 (PKD1) activation, which is capable of weakening the oncogenic signaling through MAPK and-catenin[137] and later inhibiting prostate cancer growth.[137] There was also a notable PKD1 downregulation following the progression of androgen-dependent to androgen-independent prostate cancer[137] which affected the motility and invasiveness of prostate cancer by interacting with E-cadherin.[130] Therefore, it has been considered as a novel target for cancer treatment in general and specifically for prostate cancer. [138] In addition to curcumin, certain of the curcumin derivatives have also shown anti-cancer activity against prostate cancer. Surprisingly, metallo-curcumin conjugated DNA complexes displayed significant toxicity towards prostate cancer cells (DU145, LNCaP, TRAMP-C1, 22Rv1, and PC3).[85] In androgen-dependent prostate cancer, dimethyl curcumin (ASC-J9) had good activity in promoting androgen receptor degradation.[139,140]

The effect of Curcumin against the toxic impacts of radiotherapy (rt) and chemotherapy: - Radio-sensitization is commonly employed to enhance cell death in tumoral tissues.[141] Curcumin has exhibited beneficial results from the complications related to RT, including dermatitis, pneumonitis, cataractogenesis, neurocognition, myelosuppression, secondary tumor, and mucositis.[142,143] Nearly all of the aforementioned side effects are inflammatory in nature, since a strong anti-inflammatory agent, curcumin may reduce inflammatory molecule production and enhance antioxidant activity.[144] The reduction in moist desquamavention in RT-treated breast cancer patients, following oral consumption of curcumin, gives protective evidence against radiotoxicity.[142] Irradiation with curcumin reduced the incidence of cataract from 100% to 40%. High intake of curcumin is connected with a low rate of a number of neurogenic diseases. Pre-RT curcumin administration has also exhibited better outcomes in post-RT memory functional tests in mouse model. [142,145] Curcumin also protects lymphocytes, the most RT-sensitive blood cells. It is clearly known that high proliferating index of mucosal cells are prone to RT-caused damage. Intestinal mucosal was proven to be better protected in the rats which were fed curcumin, as shown in one study.[142] Additionally, another harmful effect of RT, mucositis, was also proven to decrease in rats fed curcumin.[146] PTX is a well-known chemotherapeutic agent that can produce up to 57%–83% peripheral neuropathy in breast cancer patients, leading to hair loss, joint and muscle pain, edema, vomiting, etc.[147,148] The co-administration of PTX and curcumin showed enhanced growth inhibition, apoptosis, and antimigratory activity, reflecting a synergistic effect. The apoptotic induction mechanism was found to occur through an increase in ROS production, downregulation, and upregulation of Bcl-2 and Bax, respectively. The same research further reported that curcumin has the ability to inhibit PTX-induced EGFR, ERK1/2, and Akt expression in cancer cell.[149] In the same manner, PTX and curcumin were more effective in suppressing tumor size due to inhibition of some markers, including protein kinase C, telomerase, NF-κB, and histone deacetylase in mice model.[150] Another study indicated that the combination of PTX and curcumin is able to reverse drug resistance and reduce the IC50 dose from 14.9 to 9.4μg/mL in MCF-7cells.[151]

Clinical Trials of Curcumin Nanoformulations: - Until now, there have been various studies conducted to examine the safety, pharmacokinetic features, and effectiveness of curcumin in curing human disorders. Clinical trials have indicated some promising results, as curcumin may stop or even hinder the formation of cancer cells. There are approximately 210 clinical trials of the use of curcumin that have been reported. Out of these, 92 clinical studies were completed, and the status of 32 clinical trials is unknown. The other clinical trials are at different stages of recruitment (active or not recruiting), suspension, termination, completion, and withdrawal. Numerous clinical trials have demonstrated that nanocurcumin is effective in the treatment of ankylosing spondylitis, multiple sclerosis, amyotrophic lateral sclerosis, chronic kidney disease, metabolic syndrome patients, and malignancies.[152] An investigational clinical trial conducted by Ahmadi and colleagues showed that nanocurcumin offers safe and effective therapy to individuals afflicted with amyotrophic lateral sclerosis.[153] Nanocurcumin, based on the results of another clinical trial by Dolati et al., is capable of reconstituting the rate as well as the activity of Treg cells in patients with multiple sclerosis.[154]

Conclusion and future aspects: - Curcumin has demonstrated major anticancer activity against numerous in vitro and in vivo models of cancer. Its safety and efficacy in cancer patients, both as a monotherapy or combined with other anticancer drugs, have also been fruitful. Various molecular pathways, including MAPK, EGF, NF-κB, PKD1, COX-2, STAT3, TNF-α, I-K are proposed to be inhibited or activated by curcumin. Yet, its low water solubility, low oral bioavailability, low cellular uptake, and low molecular stability restrict its anticancer activity. Because of the poor efficacy of curcumin and its derivatives, higher doses must be administered to achieve a therapeutic effect, increasing the risk of side effects and lowering patient compliance. A number of natural or synthetic polymers, lipids, or proteins have been used to deliver curcumin to cancer cells, enhancing its stability and/or cellular uptake. Numerous drug delivery approaches have enhanced curcumin's cellular uptake and efficacy. Nonetheless, the majority of these formulations remain at the proof-of-concept level and are yet to be tested under

clinical trials. There are inadequate clinical studies conducted to establish their efficacy and safety in humans. Also, a lot of the curcumin drug delivery methods that are under development are tissue-non-specific. As such, one should also address improving tissue specific delivery. Certain unwanted effects such as DNA damage, neuroinflammation, allergic response, and excitotoxicity have been reported as a result of nano-based drug delivery systems involving curcumin being toxic. Therefore, preclinical and clinical trials are required to support curcumin nano-drugs' mode of action through their pharmacokinetics and pharmacodynamics. The hour of the need is synthesizing a delivery system that would be able to target specific tissues, raise the concentration of drugs locally at the site of action, improve therapeutic efficacy, and reduce side effects of potential curcumin applications in clinics.

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