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# A REVIEW ON CHEMISTRY, BIOAVAILABILITY AND PHYSIOLOGICAL RELEVANCE OF IN-VITRO CANCER PREVENTIVE ACTIVITIES OF CURCUMIN AND NANO CURCUMIN

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**ABSTRACT:** In recent years there has been growing interest in the ability of phytochemicals which are biologically active to prevent chronic diseases such as cancer. Phytochemicals have been found to modulate the expression or activity of a large number of cellular proteins which are key for cell survival and the transformed phenotype. In this review we have attempted to address this concern to optimize the design of chemo preventive treatment by using nanocurcumin. It is important to determine which of the many reported mechanisms of action are chemically relevant. In this we consider the structure mechanisms, limitations of curcumin of a phytochemical which has very much potential against cancer. In this review we also consider the *in vitro* studies have provided useful insight into their mechanisms of action in humans. Curcumin can also sensitize tumors to chemotherapy and radiation. Clinical trial suggests that curcumin has activity against human head squamous cell carcinoma (HNSCC), colorectal cancer, hepatic cancer, oral cancer, mantle cell lymphoma and other various type of cancer. This review discusses the preventive and therapeutic potential of curcumin against cancer. Studies in humans reveal that oral administration of curcumin furnishes very low systemic levels of curcumin mostly in the low nanomolar range, so in this review study we also concentrated nanoparticle encapsulated curcumin may provide an alternative means to increase the bioavailability and also enhance the efficacy of its therapeutic effect.

**KEYWORDS:** Curcumin, Nano curcumin, Cancer

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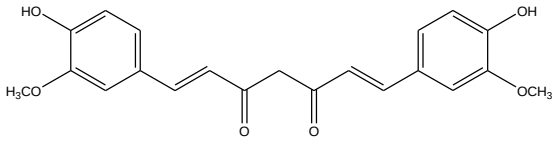
## 1. INTRODUCTION

Cancer is the one of the leading cause related to deaths in the world. Recent studies have also demonstrated promising interaction between curcumin and established chemotherapeutic agents. Accumulating evidence suggest that curcumin has a diverse range of molecular targets, supporting the concept that it acts upon numerous biochemical cascades. This polyphenol modulates various targets through direct interaction or modulation of gene expression. A key transcription factor regulated by curcumin is nuclear factor –kB(NF-KB), which is constitutively expressed in almost all cancer types and suppresses apoptosis in various tumors. Earlier studies show that this potent anti-inflammatory agent has potential for preventing and treating cancer. It can be used as a chemo sensitizing agent and radio sensitizing agent against cancer

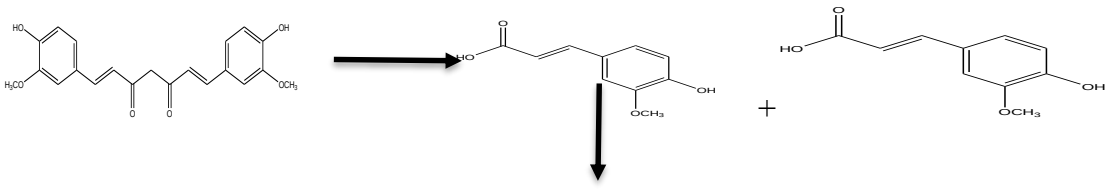
### 1. Chemistry of curcumin

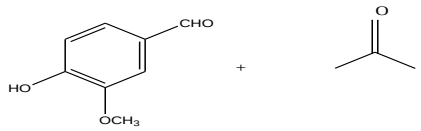
Curcumin percentage is about 3-5% in turmeric which is commonly known as Indian saffron, yellow root, dacha haldi, manjal, or natural yellow. This polyphenol was first isolated in 1815 and was obtained in crystalline form in 1870. Curcumin is an orange yellow crystalline powder, naturally obtained from the plant Curcumin longa which belongs to Zingiberaceae family in India which is also cultivated in Southeast Asian countries [1]. Turmeric that is ground rhizome of curcumin longa L has long been used in food as a spice, mainly as an ingredient in many varieties of curry powder and sauces, where curcumin from turmeric is a main coloring substance. Curcumin the product obtained by the solvent extraction of turmeric and the purification of extract is by crystallization. Turmeric is subjected to solvent extraction by using the following solvents as suitable for the extraction are acetone, $CO_{2,\ ethyl}$ acetate, dichloromethane, n-butanol, methanol and hexane. It is recovered from the extract by evaporation Curcumin is 1, 7-bis-[4-hydroxy-3-methoxy-phenyl] –hepta-1, 6-diene-3, 5-dione.Chemical formula is $C_{21}H_{20}O_6$ and its common name is feruloyl methane. Formula weight is 368 g. The structure is shown below (Figure I)




Fgure1-Curcumin structure

Curcumin is an oil soluble pigment partially insoluble in water at acidic and neutral $P^H$ and soluble in alkali. Hydrolytic degradation of curcumin (Figure-2) is feruloylmethane and ferulic acid.






Hydrolytic degradation shown above the figure-2

Degradation products formed by feruloylmethane are vanillin and acetone. In addition to curcumin, turmeric contains demethoxy curcumin and bisdmethoxy curcumin. Cyclo curcumin is another novel analogue recently identified in turmeric. Commercially available curcumin contains approximately 77% curcumin, 17% demethoxy curcumin, and 3%bisdemethoxy curcumin. Although curcumin was found to be the most potent of the three [1]. Curcumin is stable in dry food. It is relatively stable to heat so it can be used in thermally treated foods. Reported reactions of curcumin with food constituents are bleaching of color by $SO_2$ at levels in excess of 100ppm and formation of complexes with some salts such as citrate and phthalate. Curcumin has very powerful antioxidant effect and was eight times more powerful than vitamin E. Curcumin proved significantly more effective than other species in its ability to prevent lipid peroxidation. The antioxidant property of curcumin can prevent rancidity of foods and provide food stuffs containing less oxidized fats or free radicals. The powerful antioxidant property of curcumin has an important role in keeping curry for a long time without it turning rancid [2].

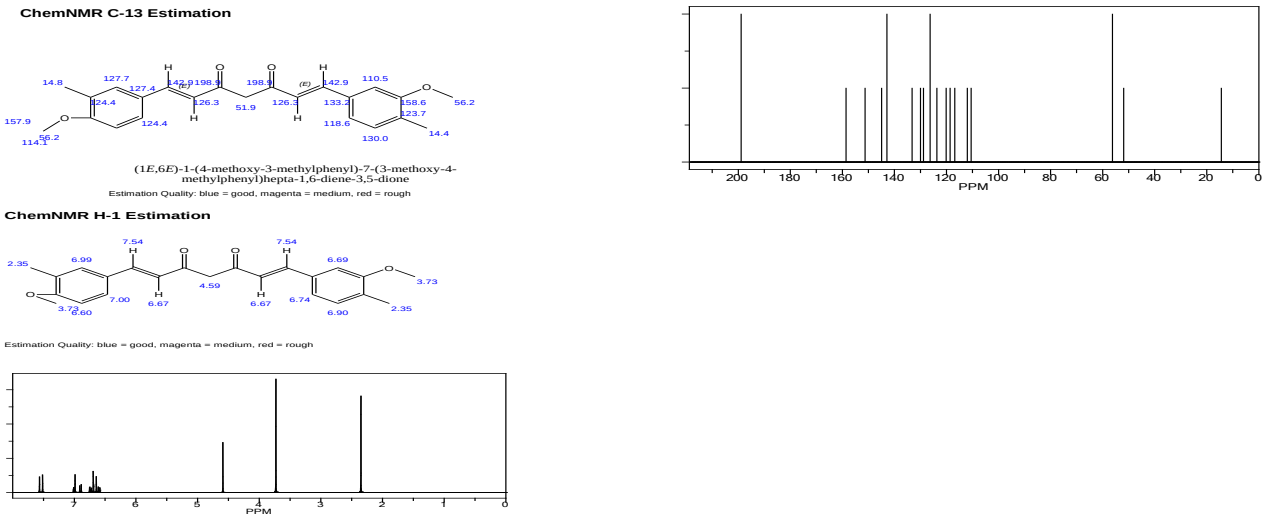



Figure-2: $C^{13}$ NM and $H^1$ NMR data and graph

Limitations of cur cumin

Prime limitations associated with curcumin are low solubility, rapid hydrolytic degradation and poor bioavailability [3]. Majority of the cancer cells show resistance towards most conventional chemotherauptic agents including curcuminoids due to over expression of drug efflux ATP –binding cassette transporter proteins including P-glycoprotein, multi drug resistance protein -1(MDRP-1), multidrug resistance protein 2(MDRP 2), and cancer resistance protein 2(BCRP), which drive the drug out of cancer cells and decrease intracellular drug concentration. Similarly, most

chemotherauptic agents including cur cumin experience lack of cancer cell targeting, lack of aqueous solubility, rapid clearance systemic circulation, intestinal metabolism and hepatic metabolism [4]. The limitations hinder the clinical usefulness of cur cumin in the treatment of multi drug –resistant cancers. The Proposal of dual drug loaded nanoparticulate combination is expected to reverse the multidrug resistance, prevent the rapid systemic clearance, prevent intestinal and hepatic metabolism, increase the aqueous solubility, enhance the bioavailability, target cancer cells, produced synergistic anticancer effect and enhance the efficacy of cur cumin in the treatment of multidrug resistant cancers to overcome.

**Anticancer properties of curcumin:** Curcumin a yellow poly phenol extracted from the rhizome of turmeric (curcumin longa L) has potent anti-cancer properties as demonstrated in plethora of human cancer cells line and animal carcinogenesis model. Nevertheless, wide spread clinical application of the relatively affrications agent in cancer and other diseases has been limited due to poor aqueous solubility and consequently minimal systemic bioavailability [5]. Nano curcumin demonstrates comparable invitro therapeutic efficacy to free curcumin against a panel of human pancreatic cancer cell lines; as assessed by cell viability and clonogenicity assays in soft agar. Nanocurcumin like free curcumin is readily disposed in aqueous media. Polymeric nano particle encapsulated formulation of curcumin-Nanocurcumin utilizing the micellar aggregates of cross-linked and random copolymers of N-isopropyl acrylamide(NIPAAN) with N-vinyl-2-pyrrollidone (VP) and poly (ethylene glycol) monoacryalte (PEG-A), physical and chemical characterization of the polymeric nanoparticles by dynamic laser light scattering and TEM (Transmission electron microscopy) confirms a narrow size distribution in the 50 nm range [5][6]. The main problem associated with the use of curcumin as a chemo preventive agent in human is its low absorption from the gastrointestinal tracts, poor solubility and effectiveness of curcumin in vivo. Current studies are under way to overcome these limitations. Curcumin nanoparticle coated with albumin – Nanocurcumin – give very good results in the prevention and treatment of breast cancer [7]. Earlier studies have shown that Nanocurcumin has efficient anticancer effect as compared to normal curcumin. Nanotechnology based drug delivery systems have shown that the efficacy of normal drug can be improved by Nano-formulation. In the case of curcumin for the treatment of cancer, clinical application of dietary curcumin has poor efficacy due to low bioavailability as well as rapid metabolism and elimination from body. Multifunctional polymeric Nanocurcumin have shown an improved therapeutic effect for cancer therapy [8]. Curcumin a greatly potent nontoxic and naturally existing bioactive material in turmeric is widely used to develop biomedical material in turmeric is widely used to develop biomedical material which are friendly to nature and environment .Aqueous based Nanocurcumin which are prepared green process that is curcumin impregnated gelatin cellulose fibers are superior performer against E. Coli and S.aureus antimicrobial study than normal

impregnated gelatin cellulose fibers[9].Nanocurcumin formulations has very good potential against, macro filarial, anti-wolbachial activity over free curcumin. In vitro studies have shown that the nano curcumin is a novel ant filarial agent with DNA topoisomerase-II inhibition activity [10]. Nanocurcumin particles prepared by top-down method with particle size less than 1000nm in diameter can improve hydrophobicity and increase bioavailability. Mice which have $CCl_4$ induced hepatic fibrosis can be treated with the above nano particles Studies had shown that mice were recovered from hepatic fibrosis after four weeks. The results show that Nanocurcumin have significant effect on reducing levels of serum alanine aminotransferase ($_{A4LT}$) and aspartate aminotransferase (AST) [11]. To enhance the bioavailability poorly soluble medicinal herbs such as curcumin in the body, Nanocurcumin solid dosage formulations were prepared and studied for its dissolution behaviour. Nano crystal loaded solid dosage drug forms have improvement in the dissolution behavior [12]. By simple sono chemical method nanostructured phyto drugs such as curcumin quercetin can be prepared and studied their bioactivities. These nanostructured drugs are identical with their micro structured one. SEM analysis reveals that the nano forms are like nano cubes and like nan needles These particles exhibit significantly high DNA binding from DNA interaction studies and CD spectral changes observed for the nano curcumin reveal its penetration into the core of the DNA through the minor grooves where it forms H-bonds with nitrogen/oxygen atoms of the DNA bases [13]. Nanocurcumin formulations were prepared by dissolving PLGA merged in acetonitrile lipids such as DMPC and DMPG were mixed in different molar ratios and volumes was made up to 1mL to obtain hybrid nonfarm[14] In the comparative study of the formulation and characterization of curcumin nanoparticles using two poly(lactyl-co, glycolide) (PLGA) combinations 50:50 and 75:25 having different lactide to glycolide ratios shows that nano curcumin 50 :50 showed smaller size and higher encapsulation efficiency than 75:25. Nanocurcumin with PLGA 50:50 has potential effect on anti-cancer activity than normal curcumin. Curcumin has the efficiency to enhance the efficacy of existing chemo preventive agent, Curcumin and nano curcumin has potential effect in the treatment breast cancer [15]. Design and development of nanoparticle self-assemblies, nanogels, liposomes, and complex fabrication for sustained efficient curcumin delivery which control the cancer cell growth, inflammation, invasion, apoptosis revealing its anticancer potential [16]. The synthesized cationic poly (butyl) cyanoacrylate (PBCA) nanoparticles are coated with chitosan encapsulated formulation of curcumin –Nanocurcumin has been shown to exhibit antigenic biomarkers vascular endothelial growth factor (VEGP) and cyclooxygenase-2 (cox-2) expression. In future Nanocurcumin can be used for heptao cellular carcinoma (HCC) 17].

**2) Nano drug delivery**

Over the last few decades, colloidal drug delivery systems have been developed in order to improve the efficiency and the specificity of drug action [18]. Gold nanoparticles provide non-toxic carriers for drug and gene delivery applications. With these systems, the gold core imparts stability to the assembly, while the monolayer allows tuning of surface proper- ties such as charge and hydrophobicity. Another attractive feature of gold nanoparticles is their interaction with thiols, providing an effective and selective means of controlled intra- cellular release which targeted and concentrated drugs using a Ferro fluid cluster composed of magnetic nanoparticles. The potential of magnetic nanoparticles stems from the intrinsic properties of their magnetic cores combined with their drug loading capability and the biochemical properties that can be bestowed on them by means of a suitable coating. CNT has emerged as a new alternative and efficient tool for trans- porting and Trans locating therapeutic molecules. CNT can be functionalized with bioactive peptides, proteins, nucleic acids and drugs, and used to deliver their cargos to cells and organs. Because functionalized CNT display low toxicity and are not immunogenic, such systems hold great potential in the field of nanobiotechnology and nanomedicine [19] Pastorin et al. have developed a novel strategy for the functionalization of CNTs with two different molecules using the 1, 3-dipolar cycloaddition of azomethine ylides [20]. The attachment of molecules that will target specific receptors on tumor Cells will help improve the response to anticancer agents. Liu et al. have found that prefunctionalized CNTs can adsorb widely used aromatic molecules by simple mixing, forming "Forest–scrub"-like assemblies on CNTs with PEG extending into water to impart solubility and aromatic molecules densely populating CNT sidewalls. The work establishes a novel, easy- to-make formulation of a SWNT-doxorubicin complex with extremely high drug loading efficiency [21]. In recent years, graphene based drug delivery systems have attracted more and more attention. In. first reported, application of nanoparticle was nano-graphene oxide (NGO) for cellular imaging and drug delivery [22]. They have developed functionalization chemistry in order to impart solubility and compatibility of NGO in biological environments. Simple physic sorption via π-stacking can be used for loading doxorubicin, a widely used cancer drug onto NGO functionalized with antibody for selective killing of cancer cells in vitro. Functional nanoscale graphene oxide is found to be a novel nanocarrier for the loading and targeted delivery of anticancer drugs [23]. Controlled loading of two anticancer drugs onto the folic acid-conjugated NGO via π–π stacking and hydro- phobic interactions demonstrated that NGO loaded with the two anticancer drugs showed specific targeting to MCF-7 cells (human breast cancer cells with folic acid receptors), and remarkably high cytotoxicity compared to NGO loaded with either doxorubicin or camptothecin only. The PEGylated (PEG: polyethylene glycol) nanographene oxide could be used for the delivery of water-insoluble cancer drugs [24]. PEGylated NGO readily complexes with a water insoluble aromatic molecule

SN38, a camptothecin analogue, via non covalent van der Waals interaction. The NGO-PEG- SN38 complex exhibits excellent aqueous solubility and retains the high potency of free SN38 dissolved in organic solvents. It was found GO-Fe3O4 hybrid could be loaded with anti- cancer drug doxorubicin hydrochloride with a high loading capacity [25]. This GO-Fe3O4 hybrid showed super paramagnetic property and could congregate under acidic conditions and be redisposed reversibly under basic conditions. This pH-triggered controlled magnetic behavior makes this material a promising candidate for controlled targeted drug delivery Nano-fomulation of curcumin with a tripolymeric composite, that is encapsulation with a tripolymeric composite, that is encapsulation of curcumin in alginate –chitosan-pluronic composite nanoparticle is used for delivery to cancer cells. The composite nanoparticle was prepared by using three biocompatible polymers alginate (ALG), chitosan (CS) and pluronic by ionotropic pre gelation followed by poly cationic cross linking pluronic 127 was used to enhance the solubility of curcumin in the alginate-chitosan pluronic nanoparticles. The size of the nanoparticle, with an average size of 100 +/- 20 nm was confirmed by AFM and scanning electron microscope (SEM) analysis. The potential interaction of among the constituent's composites nanoparticles at a concentration 500mg/ml were nontoxic to Hela cells. Cellular internalization if curcumin loaded composite nanoparticle was confirmed from the green fluorescence inside Hela cells [26]. Curcumin loaded chitosan /poly (butyl cyanoacrylate) nanoparticle were synthesized and *in vitro/in vivo* anticancer evaluation were carried out. Curcumin nanoparticle were synthesized by using cationic poly (butyl) cyanoacrylate nanoparticle coated with chitosan. The size and zeta potential of the nanoparticle were about 200 nm and +29.11mv having 90. 04encapsulationefficiency.Conformation of nanoparticle was done by using TEM. Curcumin nanoparticles demonstrate comparable invitro therapeutic efficacy to free curcumin against human hepatocellular cancer cells lines as assed by cell availability and pro apoptotic effects. In vivo studies showed that curcumin nanoparticles suppressed hepatocellular carcinoma growth and inhibited tumor angiogenesis [27].

**Cancer Therapy**

A new initiative, which takes advantage of several properties of certain nanofluids to use in cancer imaging and drug delivery is there. This involves the use of iron-based nanoparticles as delivery vehicles for drugs or radiation in cancer patients. Magnetic nanofluids are to be used to guide the particles up the bloodstream to a tumor with magnets. It will allow doctors to deliver high local doses of drugs or radiation without dam- aging nearby healthy tissue, which is a significant side effect of traditional cancer treatment methods. In addition, magnetic nanoparticles are more adhesive to tumor cells than non- malignant cells and they absorb much more power than micro particles in alternating current magnetic fields tolerable in humans; they make excellent candidates for cancer therapy. Magnetic nanoparticles are used because as compared to other metal-type nanoparticles,

these provide a characteristic for handling and manipulation of the nanofluid by magnetic force [28]. This combination of targeted delivery and controlled re- lease will also decrease the likelihood of systemic toxicity since the drug is encapsulated and biologically unavailable during transit in systemic circulation. The nanofluid containing magnetic nanoparticles also acts as a super-paramagnetic fluid which in an alternating electromagnetic field absorbs energy producing a controllable hyperthermia. By enhancing the chemotherapeutic efficacy, the hyperthermia is able to produce a preferential radiation effect on malignant cells 3030[29]. There are numerous biomedical applications that involve nanofluid such as magnetic cell separation, drug delivery, hyperthermia, and contrast enhancement in magnetic resonance imaging. Depending on the specific application, there are different chemical syntheses developed for various types of magnetic nanofluids that allow for the careful tailoring of their properties for different requirements in applications. Surface coating of nanoparticles and the colloidal stability of bio- compatible water-based magnetic fluids are the two particularly important factors that affect successful application [30] [31]. Nano fluids could be applied to almost any disease treatment techniques by reengineering the nanoparticles' properties. In their study, the nanoparticles were laced with the drug docetaxel to be dissolved in the cells' internal fluids, releasing the anticancer drug at a predetermined rate. The nanoparticles contain targeting molecules called aptamers which recognize the surface molecules on cancer cells preventing the nanoparticles from attacking other cells. In order to prevent the nanoparticles from being destroyed by macrophages—cells that guard against foreign substances entering our bodies the nanoparticles also have polyethylene glycol molecules. The nanoparticles are excellent drug-delivery vehicles because they are so small that living cells absorb them when they arrive at the cells' surface. For most biomedical uses the magnetic nanoparticles should be below 15 nm in size and stably dispersed in water. A potential magnetic nanofluid that could be used for biomedical applications is one composed of FePt nanoparticles. This FePt nanofluid possesses an intrinsic chemical stability and a higher saturation magnetization making it ideal for biomedical applications. However, before magnetic nanofluid can be used as drug delivery systems, more research must be con- ducted on the nanoparticles containing the actual drugs and the release mechanism. Cancer is a hyper proliferative disorder that is usually treated by chemo therapeutic agents that are toxic not only to tumor a cells but also to normal cells, so these agents produce major side effects in addition these agents are highly expensive and thus not affordable to most. Moreover, such agents cannot be used for cancer prevention. Curcumin a component of turmeric is one such agent that is safe affordable and efficacious curcumin modulates growth of tumor cells through regulation of multiple cell signaling path ways including cell proliferation pathway. (Cyclin. D, C-myc), cell survival pathway (Bcl-2, Bal-XL, Cu LIP, XIAP, C-/API) capase activation pathway (capase-8, 3, 9) tumor suppressor pathway (JNK, Act and AMPK) [1] (Anand P et al 2008). Curcumin has been shown to

interfere with multiple cell signaling pathways including cell cycle (cycliln DI and cyclin E), apoptosis ( activation of cases and down-regulation of antiapoptotic gene products) proliferation (HER-2m EGFR and AP-1) survival (PIZK/AKT pathway), invasion (MMP-9 and adhesion modules), angiogenesis (VEGF) ,metastasis (CXCR-4) and inflammation (NF-kappa B TNF, IL-6,Il-1, COX-2 and 5-LOX).The activity of curcumin reported against leukemia and lymphoma, gastrointestinal cancers, lead and neck squamous cell carcinoma, lung cancer, melanoma neurological cancers and sarcoma reflects its ability to affect multiple targets Thus an old age disease such an cancer requires an old age treatment[32]. Curcumin down regulates the constitutive activation of nuclear factor Kappa-B and I kappa B alpha kinase in human multiple myeloma cells, leading to suppression of proliferation and induction of apoptosis. Because of the central role of transcription factor nuclear factor kappa B (NF-kappa B) in cell survival and proliferation in human multiple myeloma (MM) NF-kappa B was constitutively active in a human MM cell lines examined and that curcumin, a chemo preventive agent, down regulated NF-kappa B in all cell lines as indicated by electrophoretic mobility get shift assay and prevented the nuclear retention of P 65 as shown by immune cytochemistry. All MM cell lines showed constitutively active I kappa B Kinase (IKK) and I kappa B alpha phosphorylation. Curcumin suppressed the constitution I kappa B alpha phosphorylation through the inhibition of IKK activity. Curcumin also down regulated the expression of NF-kappa B regulated gene product including I kappa B alpha, Bcl-2Bcl-α(L), cyclin D, Interleukin-6. This led to the suppression of proliferation and arrest of cells at G (1) /s phase of the cell cycle. Suppression of NF kappa B complex by IKK gamma/NF.Kappa B essential modulator binding domain peptide also suppressed the proliferation of MM cells. Curcumin also activated capase 7 and capase 9 and induced poly adenosine-5 '– diphosphate ribose polymerizes (PARP) cleavage [6]. Curcumin is a polyphenol found in turmeric (Curcuma longa), used as a spice, in food coloring, and as a traditional herbal medicine. It has been shown that curcumin has health benefits such as antioxidant, anti-inflammatory, and anticancer properties, improvement of brain function, and control of obesity and diabetes. However, native curcumin easily degrades and has low oral bioavailability, and a recent report has expressed doubt about curcumin's various effects. To overcome its low bioavailability, various curcumin formulations with enhanced bioavailability are currently being developed [33]. Most of these benefits can be attributed to its antioxidant and anti-inflammatory effects. Ingesting curcumin by itself does not lead to the associated health benefits due to its poor bioavailability, which appears to be primarily due to poor absorption, rapid metabolism, and rapid elimination. There are several components that can increase bioavailability. For example, piperine is the major active component of black pepper and, when combined in a complex with curcumin, has been shown to increase bioavailability by 2000%. Most of these benefits can be attributed to its antioxidant and anti-inflammatory effects. Ingesting curcumin by

itself does not lead to the associated health benefits due to its poor bioavailability, which appears to be primarily due to poor absorption, rapid metabolism, and rapid elimination. There are several components that can increase bioavailability. For example, piperine is the major active component of black pepper and, when combined in a complex with curcumin, has been shown to increase bioavailability by 2000[34]. Natural products serve as a key source for the design, discovery and development of potentially novel drug like candidates for life threatening diseases. Curcumin is one such medicinally important molecule reported for an array of biological activities. However, it has major drawbacks of very poor bioavailability and solubility. Alternatively, structural analogs and degradants of curcumin have been investigated, which have emerged as promising scaffolds with diverse biological activities. Dehydrozingerone (DZG) also known as feruloylmethane, is one such recognized degradant which is a half structural analog of curcumin. It exists as a natural phenolic compound obtained from rhizomes of Zingiber officinale, which has attracted much attention of medicinal chemists [35]. The synthesized Curcumin and its ten derivatives and evaluated as cytotoxic and antioxidant agents. The results of primary screening by Sulforhodamine B assay against five human cancer cell lines (U-251 MG, glioblastoma; PC-3, human prostatic; HCT-15, human colorectal; K562, human chronic myelogenous leukemia; and SKLU-1, non-small cell lung cancer) allowed us to calculate the half maximal inhibitory concentration ($IC_{50}$) values for the more active compounds against HCT-15 and K562 cell lines. Some Compounds were the most active against both cell lines and were more active than curcumin itself [36]. Earlier reports show that curcumin has potential anti-cancer properties. But the property of curcumin is limited due to its poor aqueous solubility and low systematic bioavailability. To overcome this limitations nanoparticle based drug delivery approaches are developed. Synthesis of polymeric nanoparticle encapsulated formulation of curcumin- nanocurcumin, using micellar aggregated of cross linked and random copolymers) demonstrate comparable in vitro therapeutic efficacy to free curcumin against human pancreatic cancer cell lines [5]. Series of curcumin derivatives/analogues were designed and synthesized by efficient methods. All the synthesized compounds have been screened for their cytotoxicity and evaluated their antioxidant activity. Cytotoxicity effect has been evaluated against three cell lines Hep-G2, HCT-116 and QG-56 by MTT assay method. Structure activity relationship has revealed that particularly, compound 3c, (IC50 value 6.25 μM) has shown better cytotoxicity effect against three cell lines. According to results of SAR study, it was found that 4H-pyrimido[2,1-b] benzothiazole derivatives, pyrazoles benzylidene, exhibited better antioxidant activity than curcumin. A correlation of structure and activities relationship of these compounds with respect to drug score profiles and other physical-chemical properties of drugs are described and verified experimentally [37]. Curcumin and its derivatives have been extensively studied for their remarkable medicinal properties, and their chemical synthesis has been an important step in the

optimization of well-controlled laboratory production. A family of new compounds that mimic the structure of curcumin and curcuminoids, here named retro-curcuminoids, was synthesized and characterized using 1D $^{1}$H- and $^{13}$C-NMR, IR, and mass spectrometry; the X-ray structure of some structures are reported here for the first time. The main structural feature of these compounds is the reverse linkage of the two aromatic moieties, where the acid chloride moiety is linked to the phenolic group while preserving α, β-unsaturated ketone functionality. The cytotoxic screening of of some structures at 50 and 10 μg/mL was carried out with human cancer cell lines K562, MCF-7, and SKLU-1. The molecular resemblance to curcuminoids and analogs with ortho substituents suggests a potential source of useful bioactive compounds [38]. The main problem associated with the use of curcumin as a chemo preventive agent in human is its low absorption from the gastrointestinal tract, poor solubility and effectiveness of curcumin invivo. Curcumin nanoparticles coated with albumin- nanocurcumin give very good results in the prevention and treatment of breast cancer [7]. Shehzad et al showed earlier studies of nanocurcumin has efficient anti-cancer effect as compared to normal curcumin. Nanotechnology based drug delivery systems have the potential to enhance the efficacy than normal drugs. In the case of curcumin for the treatment of cancer, clinical application of dietary curcumin has poor efficacy due to low bioavailability as well as rapid metabolism and elimination from the body. Multifunctional polymeric nanocurcumin have been shown an improved therauptic effect for cancer therapy [8]. Curcumin a greatly potent nontoxic and naturally existing bioactive material in turmeric is widely used to develop biomedical material which are friendly to nature and environment. Aqueous based nanocurcumin which were prepared by green process impregnated gelatin cellulose fibers are superior performer against E. coli and S. aureus (anti-microbial study) than normal curcumin impregnated gelatin cellulose fibers [9]. It has been shown that nanocurcumin is a novel anti-filarial agent with DNA topoisomerase II inhibiting activity. Nanocurcumin formulations has very good potential against muro filarial, macro filarial and anti wolbachial activity over free curcumin [10]. Nanoparticle prepared by top down method with particle size less than1000nm in diameter can improve hydrophilicity and increase bioavailability. Hepatic fibrotic livers of mice treated with the above nanoparticles were recovered after four weeks. The results show that the nanocurcumin have significant effect on reducing levels of serum alanine aminotransferase(ALT) and aspartate amino transferase (AST)[11]. It was reported that nanocurcumin solid dosage formulations such as nanocrystal loaded solid dosage drug forms have improvement in the dissolution behavior. Thus we can enhance the bioavailability of poorly soluble medicinal herbs such as curcumin in the body [12]. By simple sonochemical method nano structured photo drugs such as curcumin –quercetin was prepared and studied [12]. These nano structured drugs are identical with micro structured one and exhibits significantly high DNA binding interaction [13]. In earlier studies the prepared nano curcumin formulations by dissolving PLGA

merged in acetonitrile lipids such as DMPC and DMPG were mixed in different molar ratios and volumes was made up to 1ml to obtain hybrid nan form [14]. In the comparative study of the formulation and characterization of curcumin nanoparticles using two polys (lactide-co, glycolide) (PLGA) combinations50:50 and75:25 having different lactide to glycolide ratios shows that nanocurcumin 50:50 showed smaller size and higher encapsulation efficiency than75:25. Nanocurcumin with PLGA 50:50 has potential effect on anticancer activity than normal curcumin [40]. It was suggested design and development of nanoparticle self-assemblies, nanogels, liposomes and complex fabrication for sustained and efficient curcumin delivery which control the cancer cell growth, inflammation invasion and apoptosis revealing its anti-cancer potential [16] and that the synthesized cationic poly(butyl) cyanoacrylate (PBCA) nanoparticles are coated with chitosan encapsulated formulation of curcumin. Nanocurcumin has been shown to exhibit angiogenic biomarkers vascular endothelial growth factor(VEGF) and cyclooxygenase-2(Cox-2) expressions. In future this nanocurcumin can be used for hepatocellular carcinoma (HCC) [17). Recent studies reported that curcumin encapsulated lipopolymeric hybrid nanoparticle formulation which could protect against QT prolongation and also render increased bioavailability and stability thereby overcoming limitations associated with curcumin [41]. Many of them studied the effects of low concentrations of curcumin on human cervical cancer (HeLa) cells. They have shown for the first time that curcumin at low micro molar range may be effective against HeLa cells, which may have implications for curcumin-based treatment of cervical cancer in humans [42]. And however, there is little evidence to show that curcumin induces the formation of brown-like adipocytes and the molecular mechanisms involved remain elusive. In addition, in most experimental trials, high doses of curcumin are administered [43]. Curcumin can potentially prevent obesity by inducing browning of inguinal WAT via the norepinephrine-β3AR pathway. In the current study, they demonstrated that curcumin (50 or 100 mg/kg/day) decreased bodyweight and fat mass without affecting food intake in mice. They further demonstrated that curcumin improves cold tolerance in mice. This effect was possibly mediated by the emergence of beige adipocytes and the increase of thermogenic gene expression and mitochondrial biogenesis in inguinal WAT. In addition, curcumin promotes β3AR gene expression in inguinal WAT and elevates the levels of plasma norepinephrine, a hormone that can induce WAT browning [44]. Curcumin plays a dual modulatory role in inhibition of adipogenesis as well as induction of the brown fat-like phenotype and thus may have potential therapeutic implications for treatment of obesity. Curcumin increased mitochondrial biogenesis, as evidenced by transmission electronic microscopic detection and enhanced expression of proteins involved in fat oxidation. Curcumin also increased protein levels of hormone-sensitive lipase and p-Acyl-CoA carboxylase, suggesting its possible role in augmentation of lipolysis and suppression of lipogenesis [45]. Curcumin may serve a pivotal role in tumor suppression via the inhibition of IGF-1R-mediated

angiogenesis under hypoxic conditions [46]. It was reported for the first time spectral data of (2E, 6E)-2,6-bis (2-methoxy benzylidene) cyclohexanone (1). Structure-activity relationships revealed that the mono-carbonyl with 2, 5-dimethoxy substituted curcuminoids could be an essential for the future drugs against cancer [45,46].

## 2.CONCLUSION

Curcumin and nanocurcumin are toxicologically safe from the studies of literature. Earlier literature studies showed that the therauptic e effect of curcumin can be improved by preparing nanomaterials such as polymeric nanocurcumin, liposomes, Nano gels, nanocrystals etc. Curcumin a natural plant derived material has a wide range of pharmacological effects. But its poor solubility hence less bioavailability reduces its therauptic effects. Conjugated curcumin nanoparticle based drug delivery system can resolve the poor bioavailability generated by curcumin

## 3. ACKNOWLEDGEMENT

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