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Curcumin as natural bioactive compound of medicinal plant *Curcuma longa* to combat against different diseases

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ABSTRACT

Plants are gifts by nature as they gives alot of benefits to human race. Medicinal herb Curcuma longa has a long history of use in medicine due to its anti-inflammatory, antioxidant, analgesic, antimicrobial and against cancer progression. Turmeric contain two classes of secondary metabolites, Curcuminoids (curcumin, demethoxycurcumin and bis-demethoxycurcumin) and turmeric essential oils (TEO). Curcumin is an active constituent of it and is highly pleriopiotic molecule. It works as antimicrobial agent against different strains of fungus, bacteria and viruses by targeting their membrane efficiency and can active against various types of cancers by targeting molecular markers. This compound also shows drastic effects against various diseases like rheumatoid arthritis, neurodegenerative diseases and can also prevent selenium and ionizing radiations induced cataractogenesis. Bioavailability, stability and solubility power of curcumin is increasing as research expands by modifying it by functional groups or in combinational therapeutics. These effects are mediated through its regulation of various transcription factors, modulates mitochondrial functions, growth factors, inflammatory cytokines, protein kinases and other enzymes. Spoilage of food is also minimized by design of a papain that is immobilized in food packaging with curcumin is crosslinked and act as antimicrobial. Curcumin as natural medicinal compound is a novel targeted agent of modern era as it shows beneficial effects in different health perspectives without giving comparatively any side effects. Research reveals that it also has capability to target stem cells, restores immune system and activate self-renewal pathways. This component is easily available, safe and target different diseases at molecular level to eradicate it.

Keywords: Kupilu, Strychnine, Analytical study, Vishamushti vati, HPTLC.

INTRODUCTION

Modern world is producing many medicinal herbs which is utilized in different herbal medicines and is very extensive field of research. Inpharmacology, now a day's modern drugs gives relief as well as they have a lot of side effects that gives harm to the human body. Curcumin (diferuloylmethane, 1,7-bis[4-hydroxy-3-methoxyphenyl]-1,6-heptadiene-3,5-dione is a component of *Curcuma longa* of yellow color that is extracted by its root and gives therapeutic effects [1]. *Curcuma longa* belongs to Zingiberaceae family and have 2500 years old medicinal history [2]. In market, it is called turmeric and our ancestors grind it and use this powder on skin having, lactating mother use it by mixing in milk, spice use in cooking and also mix with aloe-vera gel [3] to act as antimicrobial in apparent infections. It needs temperature between 20 °C and 30 °C to grow [4]. Tropical and subtropical regions of world are reported for its growth. India and then China is vastly and major producers of this herb as in Asia as Turmeric have daily use as spice in food [5]. Polyphenolic component of curcumin is major attacker against different diseases. Many ROS are produced in case of different diseases as in cancer, arthritis and Alzheimer [6] and this oxidative stress is sometimes becomes lethal and cause inflammation by producing inflammatory cytokines like IL-6, IL-1 and TNF-α genes encoded by activation of nuclear factor kappa-B(NF-κB) [7]. Apoptosis is programmed cell death and different extrinsic, intrinsic mitochondrial and intrinsic endoplasmic reticulum mechanisms are involved in it but in case of diseases as in cancer these mechanisms are disrupted [8]. Angiogenesis is another factor in cancer cell proliferation where these cells have enhance permeability retention system and escapes from the immune system. Mitochondria is the power house of the cell that involves in many metabolic pathways and plays major role in inflammation, aging, cancer and neurodegeneration [9].Oxidative stress is also reported in liver diseases either due to more intake of alcohol or heavy fat containing diet [10]. Curcumin can target multiple signaling pathways and helps in cure of various cancers like gastric, pancreatic, endometrial, prostate, leukemia, breast, lungs, osteoclastoma, oral & ovarian cancer. Chemotherapy and radiotherapy is considered the effective treatment against cancer but medicinal herbs gifted by nature have such a potential to treat the dangerous diseases. Therapeutic effects also shows in other diseases also as rheumatoid arthritis, neurodegenerative diseases, musculoskeletalpain, cataractetc. and alsotargets stem cells [1].

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Antimicrobial activity also shows against standard or novel strains of bacteria, fungus and viruses. Curcumin have low bioavailability, solubility and stability. Now researchers are trying to combat all these problems by modifying it and also check it by combinational therapeutics. As when curcumin is combined with piperine, ascorbic acid it gives more beneficial results [11]. Many formulations are produced by the help of nanotechnology to decrease its size and to combine with nanoparticles to make it more effective and beneficial. In this review medicinal properties as antioxidant, anti-inflammatory, anticancerious and antimicrobial of curcumin and ways of delivery is discussed. Treatment with natural herbs is more useful and effective than modern pharmacological drugs.

Curcumin as anti-oxidant and anti-inflammatory agent

Oxidative stress is root cause of inflammation that leads to chronic diseases. Interaction of curcumin with biomolecules is by its 0-methoxyphenyl group and methylene hydrogen that donates an electron/hydrogen to ROS and acts as antioxidant confirmed by Pulse radiolysis. Depending on nature of biomolecule all the three forms of functional groups Phenolic,keto-enol tautomeric and 7 Carbon linker groups are involved in covalent and noncovalent binding while its enol form is more stable than keto form [12]. Curcumin association with diseases shown in Fig 1. Nrf-2(Nuclear factor erythroid-2 related factor) is associated in pathways like MAPK, NF-kB, PI3K and PKC. Curcuminupstream Nrf-2 and downstream ROS & TNF soit shows antioxidant activity [7]. Curcumin is a pleiotropic molecule and modulates inflammatory response by downregulates cyclooxygenase-2 activity, lipoxygenase, mitogen-activated Janus kinases and inducible nitric oxide synthase enzymes, inhibits the production of inflammatory cytokines, tumor necrosis factor alpha, interleukin (IL) -1,-2,-6,-8 and -12, monocyte chemoattractant protein (MCP) NFkB involved in regulation of inflammation, cellularproliferation, transformation and tumorigenesis and regulates activation of transcription factors such as activating protein-1 (AP-1). Curcumin blocks cytokine gene expression and downregulates intercellular signaling proteins such as protein kinase-C and inhibits cytokine production [2]. Curcumin manganese complex has higher NO scavenging activity and gives protective effect against H_2O_2 induced cell damage in NG108-15 cells. It also scavenges oxygen free radicals like super oxide anions and hydroxyl radicals that gives initiation to lipid peroxidation which plays important role in inflammation in heart diseases and cancer. Its oxygen quenching ability gives protection to skin and inhibits lipid peroxidation by enhancing activity of endogenous antioxidant enzymes, superoxide dismutase, catalase, glutathione peroxidase and glutathione-s-transferase. Curcumin also inhibits protease activatedreceptors (PAR2 and PAR4)-mediated cell activation by blocking ERK pathway and also inhibits formation of arachidonatemetabolites, secretion of lysosomal enzymes-elastase, collagenase and hyaluronidase by macrophages [13]. Curcumin as antioxidant and anti-inflammatory agent is summarized in Table 1. Inflamatory Bowel Disease is multifactorial and involved genetic, immune and environmental factors. In this there is elevated levels of IFN-γ,IL-12 and tumor necrosis factor (TNF) and is Type1 Immunity disease prototype helper cells have two sunsets TH1 and TH2. IFNγ, TNFα and TNFβ and IL-2 secreted by TH1, while the TH2 cells secrete IL-4, IL-5, IL-6, IL-10 and IL-13. There is also increased expression of IL-33 and IL-1 receptor ST2 in the serum of IBD patients. Curcumin modulates NF-κB and pro-inflammatory cytokines such as IL-1β, TNF-α and IL-6. Molecular targets for curcumin activityare NFkB, Growthfactors, proteinkinases, adhesion molecules and enzymes [14]. Pancreatitis is loss of exocrine and endocrine functions by which production of pro- inflammatory cytokines and production of oxidant species in which pain is the main symptom. In study on pancreatitis in 140 male Wistar-Albino rats, Curcumin decreases the production of pro-inflammatory cytokines such as IL-1, IL-2, IL-6, IL-8, TNF-a, IL-12 through inhibition of NFkB, AP-1, JAK-kinase, cyclooxygenase, lipoxygenase and stimulate Casp-3 activity [15]. Protein dyshomeostasis in neurodegenerative diseases as characterized by accumulation of misfolded protein aggregates within(e.g. tau from neurofibrillary tangles) and outside of cells (e.g. Neurotic b-amyloid plaques) and in Alzheimer Curcumin binds to amyloids and reduced plaques. Molecular Chaperones HSPs that play role in refolding or degrading misfolded proteins and curcumin interacts directly with HSPs and correct their levels of HSP90, HSP70, HSP6. HSP40 and also their client proteins levels as FKBP51, Cdc37, P23. In Tg2576 AD mouse model Curcumin reduces level of inflammatory cytokines IL-1b and TNFa. Curcumin reduces AP1 transcription, hyper activate JNK that reduces hyper phosphorylated tau.Curcumin express PPARg and downregulates inflammatory cytokines that are involved in tau kinase hyperactivity, ptau accumulation and oxidative damage and also reduce accumulation of soluble tau aggregates that involves in synapse loss. It reduces ptau by reducing activation of tau kinase such as JNK and GSK3b and also reduce inflammatory cytokines that activates tau kinases. Curcumin increase HO-1,a redox sensitive inducible protein that provides neuroprotection against oxidative stress. Glucose metabolism is also defective in AD, Curcumin enhance insulin signaling by stimulating Akt,reduces GSK3b activation and inhibits JNK that phosphorylates Insulin receptor substrate [16]. Psoriasis vulgaris is common inflammatory disease of nails, joints and skin and curcumin interacts with main pathogenic pathways of disease like T cell mediated inflammation by inhibiting nuclear factor kappa B(NFkB), keratinocyte proliferation, phosphorylase kinase(PhK), angiogenesis and reduces level of IL-17 and IL-22 that are prototypical cytokines secreted by T helper 17 and 22 that play a role in pathogenesis of disease [17]. In Gentamycin induced kidney mitochondrial alterations, Curcumin upregulates various cytoprotective and antioxidant proteins by activation of nuclear factor(erythroid-2)-related factor2 (Nrf2) that is basically regulator of cell antioxidant response and also modulates inflammatory response mediated by NFkB and maintains kidney mitochondrial biogenesis,structure and funtions. In LLC-PK1 cells, Curcumin conserve the PGC-1α levels that is potent inducer of mitochondrial biogenesis and increase the number of packed cristae [18]. Cardiovascular diseases is major cause of death around the world, traditional factors include age, gender, hypertension, dyslipidemia, smoking and nontraditional factor includes serum concentrations of CRP (C-reactive protein) has consistent relation with coronary heart disease and curcumin reduced serum levels of LDL and also modulates transcription factors such as NFkB that have role in inflammatory illness [19]. Solid Lipid Curcumin Formulations using Lipopolysaccharide stimulated RAW 264.7 macrophages an invitro anti-inflammatory model in which LPS increase inflammatory markers such as NO, PGE_2 and IL-6.$SLCP_s$ inhibited $PGE_2$and IL-6 in concentration dependent manner [20]. Curcumin when combined with piperine reduced the oxidative stress and inflammation in metabolic syndrome in clinical trials. Curcumin improved serum super oxide dismutase activity ($p < 0.001$), reduced malondialdehyde (MDA) ($p < 0.001$) and C-reactive protein ($p < 0.001$) concentrations and is safe, natural and effective CRP-lowering agent [54]. Curcumin and neem both are powerfulantioxidants, breast cancer MCF7 cells were treated with a-linolenic acid (0-500 μM) curcumin (0-50 μM), andneem leaf extract (0-88 μM*)* individually and also in combination with ALA and curcumin and ALA with Neem as ALA has also inhibitory effect towards MCF-7 cells. Combination treatments are less effective than individual treatments and also reduce inhibitory action of a-linolenic acid [21]. Chitosan (cationic polymer a polysaccharide derived from chitin found in crustacean shells)when complex with curcumin increases its antioxidant activity by enhancing its bioavailabilty. Curcumin is modified by attaching pendant carboxylic acid and forms monocarboxylate derivative, this modification allows conjugation of curcumin to Chitosan that is confirmed by FTIR-MS analysis and have deep orange-yellow colour. Through ester hydrolysis, covalently bound curcumin is released from complex,which results in phenol reformation that was modified to attach curcumin to polymer [6]. Cataract is major cause of eye blindness and surgery is the only effective treatment,

Curcumin+Dimethylsulfoxide+irradiation gives protective effect by increasing levels of antioxidant enzymesand reduce oxidative stress against ionizing radiation-induced cataract in lens of rats [22] and shows more anticataratctogenic activity than its degradative products (ferulic acid, cinnamic acid, vanillin and vanillic acid) [23]. Curcumin has therapeutic effects in many other diseases also as it involves in treatment and prevention of neurodegenerative diseases as anti-inflammatory in which it Inhibits NF-κB translocation, protein expression of GFAP and iNOS and AP-1 activation, decrease activation of astrocytes and microglia, reduce pro-inflammatory cytokine, alleviate loss of TH-IR fibersas antiapoptotic in which it reduces MMP loss, induce overexpression of BCl-2 and antagonize MPP+-induced overexpression of iNOS,decrease the Bax/Bcl-2 ratio, reduce the accumulation of A53Tα-synuclein,inhibit the JUN/c-Jun pathway, Block MPP(+) and also as antioxidant in which it restores MMP, increase level of Cu-Zn superoxide dismutase, suppress ROS, sustain SOD1 level, reduce the levels of p-p38, cleaved caspase-3 and quinoprotein formation, restore depletion of GSH levels, free radical scavenger, inhibit oxidative stress and the mitochondrial cell death pathway, activate the Nrf2/ARE pathway, reduce p53 phosphorylation, prevent α-synuclein aggregation and fibrillation and inhibits MAO-B activity so thatit act as neuroprotective agent [24]. Curcumin restores CD4+ and CD8+ cells that triggers release of inflammatory cytokines (IFN and IL12) these attract cells of innate immune system like NK, NKT and triggers killing of tumor cells by perforin, FASL and TRAIL activation and induce the proliferation of T cells,B cells and NK cells and also activates macrophages. Curcumin activates dendritic cells and blocked release of cytokines CD80, CD86, IL1, IL6, TNF and induce phosphorylation of MAPK [25]. By this Curcumin also restore or modulates the functionality of mitochondria by altering the production of mitochondrial ROS and inhibits organelle enzymes and regulates or starts the expression of several proteins that are involved in mitochondrial functions [9]. Pain is an unpleasant sensory and emotional experience in which tissue injury causes nociceptors to depolarize that results in activation of sensory impulses as nociceptive information impulses travels along sensory afferent fibers where they synapse on secondary neurons and interneurons.Neuropepetides and inflammatory mediators such as bradykinin, prostaglandins, proinflammatory cytokines are released at site of injury. Curcumin reduces nociception by inhibiting mRNA or protein expression of COX-2, LOX and inducible nitric oxide synthase. Also gives relieve from musculoskeletal pain that includes bone, joint and muscular tissues [26]. Turmeric uses in dentistry as mouth wash, dental plague detection system, sub gingival irritant and pit and fissure sealant in which curcumin is active compound [27] and improvement in mouth opening and burning sensation was noticed in oral sub mucous fibrosis [28]. Curcumin also shows therapeutic effects against alcohol liver disease that leads to chronic diseases as cirrhosis and fibrosis. Curcumin gives relief from oxidative damage, improves cell recovery and stops release of ALT (alanine aminotransferase) and AST (aspartate aminotransferase) so gives protection against toxic effects of alcohol use. This natural compound inhibits expression of cytokines, chemokines, COX-2, iNOS, endotoxin-mediated activation of NFkB in liver cells [10, 29].

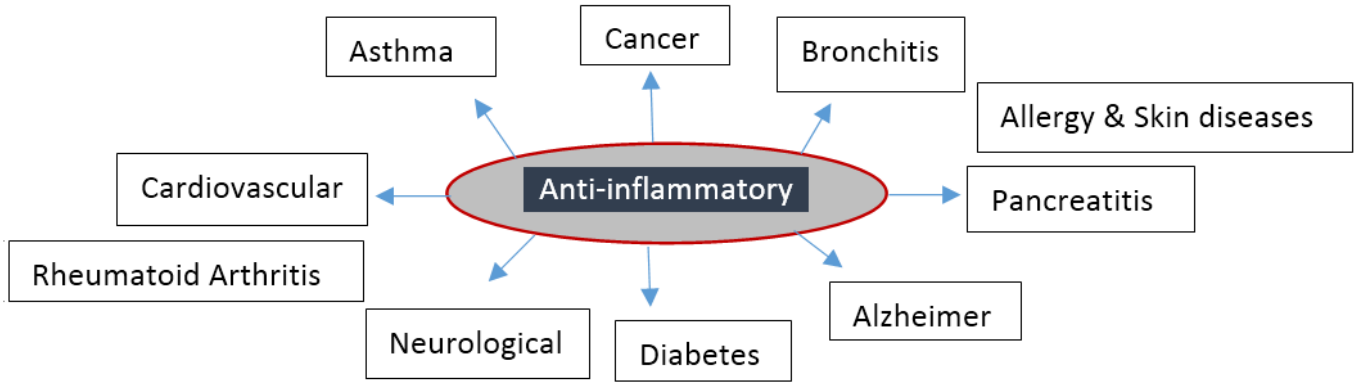

Figure 1: Curcumin as anti-inflammatory in different diseases

Table 1: Curcumin as antioxidant and anti-inflammatory agent

Curcumin As Antioxidant and Anti-inflammatory		**Ref.**
Upstream Nrf 2 & Antioxidant proteins, Downstream COX-2, LOX, iNOS, mitogen-activated, Protein Kinase-C, Janus Kinases And Inhibits TNF-a,MCP,IL ,-2,-6,-8,-12		[2]
Inhibits Lipid Peroxidation	Inhibits PAR2 & PAR4 and blocker pathway	[13]
Inflammatory Bowel Disease	Modulates NFkB,IL-1,-6,-12,IFNγ,TNF Targets: Growth factors, Kinases, Enzymes, Adhesion molecules	[14]
Pancreatitis	Inhibits NFkB, JAK-kinase, COX, LOX, AP-1 and Decreases: IL1,-2,-6,-8,-12, TNF	[15]
Alzheimer	Upregulates HO-1,Insulin signaling and inhibits JNK kinase,GSK-3B,tau while down regulating IL-1B & TNF-a	[16]
Psoriasis	Inhibits NFkB,PhK,IL 17,IL22	[15]
Mitochondrial alterations	Upregulates Cytoprotective & Antioxidant proteins,PGC-1α While accumulating Nrf2	[18]
Cardiovascular diseases	Modulates NFkB	[19]

Curcumin in treatment of Cancer

Cancer and its treatment is a huge challenge for scientific community. Natural medicine as Curcumin which is widely use especially in Asia gives drastic effects against proliferation of cancer. Polyphenoliccompound has shown therapeutic effects against colorectal, pancreatic, breast, prostate, myeloma,lung cancer as discussed in clinical trials [1]. Angiogenesis is growth of blood vessels both in health and vastly growth in different diseases like cancer, tumors, eye illness and inflammation. Formation of new tissue needs formation of new vessels as new tissue needs nutrients via blood vessels. In process of Angiogenesis different factors are involved as TGF-β1(Transforming growthfactor), FGF(Fibroblast growth factor), VEGF(vascular endothelial growth factor), PDGF(platelet derived growth factor), Ang(Angiopoietins), mTOR(Mammalian target of rapamycin), uPA(Urokinase plasminogen activator), MMPs(Matrix metalloproteinases), BAkt(Protein kinase), NOS(Nitric oxide synthase), COX-2(cyclo oxygenase-2), PKA(protein kinase A), PKC(Protein kinase C), MAP-kinase(Mitogen activated protein kinases), Nrf2(Nuclear factor(erythroid-derived 2 related factor), AP-1(Activated protein), HIF(Hypoxia inducible factor), NFkB(Nuclear factor "kappa light chain enhancer "of activated B cells), integrin's, cadherin's, fibronectin and collagen. Curcumin and its analogs inhibit these factors in diseases by directly interacting with it and stops angiogenesis as they interact with transcription factors NFkB,mTOR pathway and reduce expression of VEGF and MMP9[30]. By binding to telomeric G-quadraplexes DNA it initiates the activity of telomerases that are inhibited in cancers and stops proliferation by binding of curcumin to human telomeres sequence [31]. Breast cancer is one of the most common type of cancer all around the world and secretion of osteolytic factors(PTHrP) is important for breast cancer bone metastasis. Curcumin completely inhibit PTHrP secretion of concentration 100µM on MDA-MB-231 cells one of most studied estrogen-receptor negative human breast cancer cell lines. Degradative metabolites of curcumin vanillin and ferulic acid gives no effect but very high dose of ferrulic acid actually stimulated PTHrP secretion that gives adverse biological effect, tetrahydrocurcuminoid(reductive metabolite) inhibits PTHrP secretion but with 10-fold lower potency [32]. Curcumin decreases HER2 expression, phosphorylation of Akt, MAPK, NFkB and also deregulate expression of cyclinD1, PECAM-1 and P65 that are regulated by NFkB in breast cancer xenograft mouse model prevents angiogenesis and cause apoptosis [33]. Curcumin prevents palmitoylation of Integrin β4 in MDA-MB-231 breast cancer cells byinhibiting activity of acyl transferase DHHC3 that is required for palmitoylation in concentration of 15 µM. DHHC3 is member of palmitoyl acyltransferase family of proteins which transfers palmitoyl-CoA to cysteines of substrate proteins as this also requires an auto acylation intermediate step and also curcumin blocks auto acylation [34]. Curcumin induces TRAIL-induced apoptosis(Tumor Necrosis Factor-Related Apoptosis Inducing Ligand) by regulating apoptotic proteins (Mcl-1, ERK and Akt) on MCF-7 breast cancer cells at concentration 200µg/ml [35]. Micro RNAs are 19-25 nucleotides that do not translate to proteins but regulates gene expression by binding to complementary mRNAs and cause its degradation thus decreases protein production. Pathways associated with miR-21 are phosphatase and tensin homolog(PTEN), phosphoinositide 3-kinase/protein kinasw (PI3K/Akt), programmed cell death protein 4(PDCD4) and NFkB. Curcumin decreases miR-21 and increase PTEN expression so that decrease PI3K/Akt pathway activity which leads to decrease eIF4A and eIF4G and decreases translation so blocks NFkB. PDCD4 that is a tumor suppressor also increases by blockage of miR-21 and increase cell death through p21. Curcumin decreases miR-21 by inhibiting AP-1 to its promoter and inhibits its gene expression [36]. PTEN and LKB-1 when knocks out causes cancer and activates mTORC-1, CyclinD1, Akt and antiapoptotic BCL-2 proteins [37]. Curcumin Inhibits invitro and *in vivo* chronic myelogenous leukemia growth of cells that is cancer of white blood cells by downregulating Bcr-Abl(this oncoprotein activates several pathways that inhibits apoptosis and increases proliferation) through increase of miR-196b, downregulate VEGF and AkTphosphorylation, increase PTEN by targeting miR-21 and reduce CML cells migration in K562 & LAMA84 cells at 40µM [38]. Gastric cancer that is third in men and forth in women leading cause of deatharising from epithelial cells is one of the highly malignant carcinomain which impaired K_{ATP} channel loss the mitochondrial membrane potential. In an in vitro study on gastric cancer cell line SGC-7901 when treated with curcumin in a dose dependent manner ($P < 0.05$) inhibits the cells proliferation best at HCur (39.4%±9.43%) [39] As Voltage gated mitochondrial membrane potentials (K_v10.1 encoded by KCNH1 gene, Kv11.1 encoded by hERG1/KCNH2,K_v1.3,K_v1.5,Ca_v1,Ca_v1.3 encoded by CACNA1D, Cav3encoded by CACNA1H, Nav1.5, Nav1.6, CLC2 and CLC3) are deregulated and involved in proliferation of different cancers [40]. Extrinsic, Intrinsic mitochondrial and intrinsic endoplasmic reticulum pathways triggered apoptosis with actin rearrangement is needed. Curcumin analogue MHMD gives much better response than curcumin and induces A549 lung cancer cell apoptosis by activation of capase-3,-8,-9,-12,PARP and increase ratio of pro-apoptotic proteins Bax/Bcl-2 and causes apoptosis in concentration of 4µM [8]. Curcumin induces 85 % apoptosis in HPV16 positive oral cancer cell line 93VU147T by expression of pro-apoptotic protein Bax and downregulated anti-apoptotic markers Bcl-2 and cIAP at 100µM and also re-expresses tumor suppressor p53 that is degraded by viral E6 oncoprotein.It inhibits activation of AP-1,NFkB so that they can't bind to cis-regulatory URR of HPV that modulates E6 transcription and so suppresses transcription of E6 oncogene and also change morphogenesis of AP-1 and NFkB by changing AP-1 c-Jun/JunB to JunD/JunD homodimers and NFkB p50/p50 homodimer to p50/p65 heterodimeric DNA-binding complex [41]. In Osteoclastoma (Giant cell tumor)that is invasive primary benign bone tumor, curcumin Inhibits NFkB, MMP-9 gene expression, activates JNK signaling pathways and boost up the capase-3 activity and causes apoptosis of these Giant tumor cells in primary cell lines at 40µM [42]. Curcumin also gives its effects against pancreatic cancer in which now a date tumor removal and chemotherapy treatment is considered most effective. By this natural compound it induces expression of CELF2,down regulates survivin,cellular IAP1 and 2, XIAP, MMP-9, VEGF, Cyclin D1, COX-2, reduces NFkB and STAT3 signaling, SP1 and arrest cell cycle in G2/M phase and so regulates balance between cell survival and death [43]. Endometrial cancer is common cancer in gynecologicaldiseases. Curcumin inhibits its proliferation at 40 µM in HEC-1B cells and also suppresses expression of MMP-2, MMP-9 that plays key role in metastasis so decreases invasion and migration of cells at 30 µM and also reduced the phosphorylation of ERK1/2 in a concentration dependent manner [44] and also gives drastic effects in epithelial ovarian cancer in multiple cell lines in dose dependent concentration manner [45]. Ovarian cancer is major cause of deaths among womens.Curcumin increase expression of miR-9 in SKOV3 cell lines and inhibits proliferation, migration and invasion of ovarian cancer cells through suppression of talin 1/FAK/Akt pathway at 60 µM. It also activates capase-3 avtivity, cleaves PARP and reduces phosphorylation of Akt and FOXO1 that are involve in ovarian cancer metastasis [46]. Curcumin also has also capability to target the cancer stem cells through regulation of self-renewal behavior of the stem cells including Wnt/βcatenin, Sonic hedgehog and Notch pathways in different types of cancer in dose dependent manner [47, 48]. Curcumin targets colorectal cancer stem cells and reduce expression of markers(CD133, CD44, ALDH1, CD166)up to 80-90%.It upregulates cleaved PARP & Bax,deactivate phosphorylation of STAT3 and arrest cell cycle at G1 phase and also stabilizes expression of tumor suppressors like Pdcd4[49].Curcumin concentration for cancer cell apoptosis in some cancer cell lines is summarized in Table 2. Curcumin decrease number of cells alone and combination with 5-fluorouracil and oxaliplatin,targets colorectal cancer stem cells and reduce expression of cell associated markers ALDH and CD133 [50]. Selenite when combined with curcumin by hydrogen bonding and dimethylated curcumin by acid base interaction enhances its activity as selenium also shows anticancer effects and act as antioxidant [51].

Table 2. Curcumin concentration for apoptosis in Cancer cell lines

Curcumin In Cancer Cell Apoptosis			
Type of Cancer	Cell lines	Curcumin concentration	Ref.
Breast Cancer	MDA-MB-231	100 µM	[32]
Lung Cancer	A549	4 µM	[8]
Oral Cancer	HPV16	100µM	[41]
Osteoclastoma	Primary cell lines	40µM	[42]
Endometrial Cancer	HEC-1B cells	40µM	[44]
Ovarian Cancer	SKOV3	60µM	[46]
Chronic Myelogenous Leukemia	K562 & LAMA84	40µM	[38]

Curcumin as an Antimicrobial agent

Curcumin exhibits antibacterial, antifungal and antiviral activities in different species by its phenolic content. Interactions of its phenolic compound by hydrogen bonding and hydrophobic interactions with microbe makes it more disastrous for it [52]. Nano curcumin formulations are formed so that it have increased bioavailability and solubility of size 100-160 nm. This Nano curcumin have increased penetration rate to gram positive and gram negative bacteria and gives better antimicrobial activity than curcumin alone [53].Cyclodextrin that creates pocket for hydrophobic molecules and curcumin is combined with it also enhances its activity [54]. In study of curcumin in food microbiology as many strains of bacteria and fungus involves in spoilage of food, microcapsules formulations of curcumin are produced which gives pure antifungal and antibacterial effects against many strains [55]. In food packaging, 82-92% Papain is perfectly immobilized on polymers of ethylene and caprolactam with 50% curcumin as photocrosslinker.In it Linear low density polyethylene immobilization gives perfect antibiofilm properties against Acinetobacter species and *Staphylococcus aureus*[56]. Curcumin blocked hemagglutinated activity of paramyxovirus at 31.2 µM and inhibits plague formationthat is specific in enveloped viruses as in flaviviruses (JEV and Dengue virus), influenza A virus (H1 and H6 subtypes),vaccinia virus,NDV and pseudorabies virus at 30 µM and disrupts lipid bilayers in enveloped membrane organelles [57]. Curcumin inhibits EV71 replication and synthesis of viral proteins by suppressing ubiquitin-proteasome and increases level of p53 and p21 that are degraded in viral infection. It downregulates GBF1 (guanine nucleotide exchange factor) that is required in assembly of viral replication complex and also downregulates PI4KB that catalyzes formation of PI4P(phosphatidylinositol4-phosphate) involves in formation of replication complex. PARP-1 and capase-3 increased in this viral infection and induces apoptosis while by incubating curcumin with Vero cells infected with EV71 decreases their levels when 40 µmol/L curcumin applied at early stages of viral infection [58]. Human cytomegalovirus causes many infective diseases and curcumin also acts as antiviral against it in human embryonic lung fibroblast cells [59]. Cytokines secretion of IL-6 and TNF- α decreased in HELF cells and reduced IE and UL83 mRNA expression of HCMV and reduces viral proliferation [60]. Dengue is an emerging disease caused by dengue virus. There is a decreased production of Dengue type-2 virions and ubiquitin-proteasome system and cell viability decreased at 30µM curcumin concentration in Vero cells [61]. Curcumin is modified by silver nanoparticles to give efficient inhibition of respiratory Syntical virus infection. Ag nanoparticles directly attach to the virus and downregulates gene expression of IL-6 and IL-1β and remarkably inactivates the virus on Human laryngeal epithelial type-2 cells [62]. Oral pathogenic bacteria *Streptococcus pyogenes* causes severe human diseases as toxic-shock like syndrome and other oral bacteria *Streptococcus mutans* causes endocarditis and curcumin acts as antibacterial against these and kills 100% bacterial population in experiment [63]. Curcumin is also active against endodontic bacteria and MIC of curcumin against different strains are*Streptococcus mutans* (333.33 µg /ml), *Actinomyces viscosus* (167.67 µg /ml), *Lactobacillus casei* (125 µg /ml), *Prophyromonas gingivalis* (125 µg /ml), and *Prevotella intermedia* (208.33 µg /ml) [64].Minimum inhibitory concentration of standard bacterial strains as of *Staphylococcus aureus*(MSSA) is 219µg/ml, methicillin resistant *Staphylococcus aureus*(MRSA) 217 µg/ml, *Enterococcus faecalis*293 µg/ml, *Bacillus subtilis* 129 µg/ml, *Pseudomonas aeruginosa*175 µg/ml, *Escherichia coli*163 µg/ml and *Klebsiella pneumoniae* is 216 µg/ml [65]. Methanolic fraction of Curcuma longa extract have more potency to act as antibacterial against *Staphylococcus aureus* as this bacteria have resistant to antibiotics like penicillin and methicillin [66]. *Acinetobacter baumannii* is gram negative immunocompromised multi-drug resistance human pathogen. When curcumin is combined with epigallocatechin gallate antimicrobial activity increases that is key to develop drugs against drug resistance pathogens [67]. Periodontitis is main cause of tooth loss and curcumin shows antibacterial effect of 20 µg/mL on periodontopathic bacteria, particularly *Porphyromonas gingivalis*by inhibiting its Arg- and Lys-specific proteinases(RGP and KGP)with the exception of *A.actinomycetemcomitans*[68]. *Helicobacter Pylori* is related to gastro-duodenal diseases like ulcer and gastritis cancer and this bacteria is genetically distinct of different areas of the world. Curcumin suppresses it growth with MIC 5 µg/ml to 50 µg/ml and inhibits shikimate pathway that is involved in synthesis of important metabolites in bacteria [69]. Fungus infections is increasing day by day and can infect every part of body. Curcumin as natural and medicinal compound have potential to work against it without harming cellular structures. In *Candida albicans*, which is causative agent of lethal infections after treated with curcumin releases potassium ions from cellular membranes and loses membrane integrity as K is important for growth and survival So inhibits ATPase's, cell wall biosynthesis and disrupts^{pH} causes fungal cell death [70,71]. Curcumin and ascorbic acid together work as best antifungal agents against *Candida albicans* with MIC 0.625 and 0.3125 µg/mland against *Candida krusei* MIC is 1.25 µg/mlthan alone as Curcumin and ascorbic acid both are antioxidants and when their sum of effects combined give better results with curcumin instability at PH 7.4 minimized [72]. Curcumin shows antifungal activity against two plant pathogens *Phomopsis obscurans* and *Plasmopara viticola* at 30 µM which causes serious diseases of strawberry and grape plants having low environmental toxicity So that curcumin can also be act as leading compound for pesticides [73].

Delivery of curcumin

Curcumin shows therapeutic effects against many diseases as discussed previously but the matter of eye is the delivery of curcumin to cells. Curcumin has rapid metabolism, lowabsorption and so low bioavailability to cells [74]. Different ways are applied for it to increase its stability, solubility and bioavailability to maximize its potency and

efficiacy. k-carrageenan–chitosan dual hydrogel multilayers shell Bovine Serum Albumin gel Microcapsules are used for carrier of curcumin and gives best results in HELA cell lines and primary culture of mesenchymal stem cells so enhance its biodisponibility.Cell viability and proliferation rate decreases in it but the major drawback is that it effects both normal and tumor cells [75]. Mesoporous silica based drug delivery of curcumin against A549, MCF-7 and SKOV3 cancer cells also shows beneficial effects and silica is biocompatible to normal cells. Intracellular production of ROS,downregulation of PARP is the targets of this type of delivery against cancer cells [76]. Through single-step solid dispersion method Curcumin was encapsulated into different polymers micelles like monomethyl poly (ethylene glycol)-poly (ε-caprolactone)-poly (trimethylene carbonate)(MPEG-P(CL-co-TMC)). They increase uptake of curcumin in colorectal CT26 cancer cells and decreases angiogenesis and cells proliferation [77]. Nanotechnology is an emerging field of science and when it combines with biology in drug delivery system gives remarkable results and is another way of light of curcumin delivery. Curcuemulosomes (solid lipid nanoparticles)of 286nm have increase bioavailability of curcumin to 10,000 fold higher when checked it activity on HepG2 human liver carcinoma cell line [78] as delivery strategies increases its bioavailability [79]. Curcumin Nano formulations are prepared by usage of liposomes, polymeric nanoparticels, polymeric micelles, conjugates, cyclodextrins, solid dispersions and are tested on clinical trials which shows their high bioavailability and low metabolism [80]. Dimethyl sulfoxide (DMSO) base Nano bis-demethoxy curcumin analog is ideal therapeutic use intravenously [81]. Invertible micellar polymer Nano assemblies target human osteosarcoma MG63, KHOS, and LM7 cells and not to normal primary human osteoblast cells. It shows very good stability of micellarcurcumin, highly uptake by cells and arrest cell cycle in G1 and G2 phase [82]. Another approach of drug delivery is to form PEG-DOX-Cur prodrug nanoparticle for simultaneous delivery of doxorubicin(DOX) and curcumin(Cur) as a combination therapy to treat cancer with high loading capacity and comparatively low side effects in HepG 2 cells [83]. Halloysite nanotubes with chitosan grafting are formed for delivery of curcumin as shows increase stability, highuptake, apoptosis but shows specific toxicity against HepG2, MCF-7, SV-HUC-1, EJ, Caski and HeLa cells [84]. Different ways of its delivery like micro emulsions, Transferrin mediated solid lipid nanoparticles containing curcumin, Encapsulation of curcumin in alginate-chitosan-pluronic composite nanoparticle, Synthesis and *in vitro/in vivo* anti-cancer evaluation of curcumin-loaded chitosan/poly(butyl cyanoacrylate) nanoparticles, curcumin loaded dextran sulphate–chitosan nanoparticles, ApoE3 mediated polymeric nanoparticles containing curcumin, Lipid–polymer nanoparticles encapsulating curcumin, Curcumin-loaded guanidine functionalized PEGylated mesoporous silica nanoparticles, Curcumin loaded poly (2-hydroxyethyl methacrylate) nanoparticles from gelled ionic liquid, Liposomal co-delivery of curcumin and albumin/paclitaxel nanoparticle, Development of Curcumin nanoniosomes,Lipopolysaccharide based oral nano-carrier of curcumin, Gum arabic-curcumin conjugate micelles with enhanced loading for curcumin are there to enhance curcumin properties [85]. Encapsulation of curcumin in dendrosomes shows anticancer effects against fibro sarcoma, colon, glioblastoma, bladder, gastric, breast and hepatocellular carcinoma in *vitro* and *vivo* and gives no effects on normal cells [86]. Globular liposome of size 25-205nm, spherical micelle 10-100nm, lamellar noisome 190-1140nm, cyclic cyclodextrin 150-500nm, dendrimers 15-150nm, Nano gels 10-100nm, chitosan 100-250nm, globular gold 200-250nm, spherical solid lipid particles 50-1000nm of curcumin are formed and tested against different cancers and infections as a result of it curcumin shows enhanced bioavailability, solubility, tissue distribution and therapeutic effects [86].

CONCLUSION

Although medicinal plants have a vast research field in which detection of bioactive compounds is necessary for future perspectives. Curcumin is bioactive compound against different diseases but it also have a major flaw to use it in the field is its deliverymechanisms. Delivery ways should be modified to make it more applicable and to enhance its solubility power. When act as antioxidant and anti-inflammatory comparison of molecular targets and mechanisms must be detected in different related diseases. More analogues of curcumin can be formed by knowing its more detail structural activity against different molecular targets. Antimicrobial mechanisms must under consideration in different strains so that more potent drugs are formed. More research is required for curcumin as therapeutic agent against plant pathogens and in animal infections.

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