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Review

# A sojourn into therapeutic and nutraceutical potential of curcumin and its novel drug delivery system: Current achievements and future perspectives

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ABSTRACT

Curcumin is a polyphenol which is derived from the rhizomes of *Curcuma longa*. From the last few decades, it is utilized as a condiment, a flavouring and colouring agent in different food preparations. Owing to its potential, it also possesses anti-inflammatory, anti-hyperglycemic and neuroprotective actions and has shown preventive actions against various disorders such as cardiovascular, diabetes, brain and many more. In spite of numerous health benefits, the use of curcumin in humans for treatment of several diseases is limited owing to its poor aqueous solubility, wide-ranging first pass metabolism, rapid excretion, and subsequent low bioavailability. Various preclinical and clinical studies of curcumin have pointed out that curcumin plays a role in treatment of different disorders. However, many of the curcumin formulations do not comply much for their safety, stability and efficiency assessment. Henceforth, there is a need to search for an alternate method for successful commercialization of curcumin in a suitable dosage form. In this review we aim to summarize the mechanism of curcumin for treating different disorders and various clinical and preclinical studies conducted on curcumin polyphenol. Further, numerous studies have done in the past to improve its solubility which ultimately enhanced its bioavailability and therapeutic effectiveness have also been summarized.


## 1. Introduction

Curcumin, a low molecular weight hydrophobic polyphenol is a derivative of turmeric rhizomes *Curcuma longa*. From almost last 8 decades, it is utilized as a condiment, a flavouring and colouring agent in different food preparations. *Curcuma longa* consists of three lipophilic curcuminoids in the ratio of 77:17:3 as curcumin: demethoxycurcumin: bisdemethoxycurcumin, respectively. Among these curcuminoids, curcumin is the most potent one and henceforth utilized for anti-inflammatory, anti-hyperglycemic and neuroprotective actions. But in comparison to each constituent used alone, the nematocidal actions are enhanced when used in combination.

Over the past 8 decades curcumin has shown numerous disease preventing actions against disorders such as brain disorders, rheumatoid arthritis (RA), diabetes mellitus (DM), cardiovascular disorders (CVDs) and cancer (Nayak et al., 1948; Noorafshan and Ashkani-Esfahani 2013, Liu and Hou 2018). This polyphenol also shows protective effects against development of cataract, pulmonary toxicity, hepatic damage, and can impede blood coagulation and decrease the accumulation of platelets too (Ma et al., 2019). Curcumin also shows potential activity to treat different malignancies such as sarcoma, breast, genito-urinary, and other cancers (Duvoix et al., 2005). Curcumin can prevent metastatic growth of cells and increase the cell

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death by controlling various tumor necrosis receptors, proteins and enzymes (Ma et al., 2019).

Moreover, in a recent clinical study conducted by Pawar et al. in 2021 curcumin administration along with piperine resulted in quick symptomatic recovery (fever, sore throat, and breathlessness), less deterioration, improved saturation above 94%, and better clinical results as compared to control group patients (Pawar et al., 2021). Curcumin acts on different molecular pathways and reduces oxidative stress and inflammatory markers which are the root cause of many diseases (He et al., 2015; Liczbiński et al., 2020). The molecular mechanism of curcumin for treating various disorders is summarised in Table 1.

In spite of numerous health benefits, the use of curcumin in humans for treatment of several diseases is limited owing to its poor aqueous solubility, wide-ranging first pass metabolism, rapid excretion, and subsequent low bioavailability (Araiza-Calahorra et al., 2018).

To overcome this issue, numerous studies have been done in the past to improve its solubility which ultimately enhanced its bioavailability and therapeutic effectiveness. These studies focus on the preclinical and clinical evaluation of curcumin through novel drug delivery systems such as nanoparticles (NPs), liposomes, nanoemulsions, and micelles, etc. Still, many of these formulations do not comply much for their safety, stability and efficiency assessment. Henceforth, there is a need to search for an alternate method for successful commercialization of curcumin in a suitable dosage form.

The present review focuses on the different pharmacological actions of curcumin and potential role of developed formulations in overcoming the low solubility issues of curcumin (illustrated in Fig 1).

## 2. Pharmacological activities of curcumin

### 2.1. DM

DM is a chronic disease either resulting from lack of insulin production or its proper utilization, leading to altered metabolism of proteins, fats, carbohydrates, and increased blood glucose level (BGL). As per the World Health Organization (WHO) it is projected that 439 million people will be suffering from DM in 2030 (Rivera-Mancía et al., 2018). The pathophysiology of DM involves numerous signaling pathways such as production of ROS and inflammatory cytokines, upregulation of MAPK/JNK pathway, deactivation of AMPK pathway, damage of P13K/Akt signaling in adipose and skeletal muscles, and downregulation of PPAR-gamma and NF-$\kappa\beta$. Dysregulation of all these pathways leads to insulin insensitivity, IR and hyperglycaemia. All these pathways are regulated by curcumin. (Rivera-Mancía et al., 2018). DM, if left untreated leads to many complications such as DN, DCP, DNP, encephalopathy, DFU and DR..... (illustrated in Fig. 2). Several preclinical (Table 2) and clinical studies (Table 3) have demonstrated the effect of curcumin in treatment of diabetic complications and other diseases as well.

Many preclinical and clinical studies reported high potential of curcumin for DM treatment, especially for type 2 DM (T2DM). The choice of using curcumin for treating DM was initially explored by Srinivasan who discovered that 5 g of turmeric powder could significantly reduce BGL in one T2DM patient (Salehi et al., 2019). Moreover, curcumin exhibited glucose-lowering activity and reduced IR, dyslipidemia in streptozotocin (STZ) induced high fat diet (HFD) male albino Wistar rat. It also enhanced muscle and liver glycogen contents and up-regulated the gene expression of GLUT4 in comparison to the diabetic control group (Al-Saud 2019). Recently curcumin was reported to exhibit anti-diabetic effect in HFD + STZ induced diabetic rats by a decrease in the expression of suppressor of cytokine signaling 3 (SOCS3), STAT-3, as well as the increase in insulin receptor substrate-1 (IRS-1) (Zaheri et al., 2019).

Another study stated that administration of theracurmin, which is a curcumin formulation with enhanced bioavailability results in reduction of glucose intolerance in rats (Kato et al., 2017). This activity was further accompanied by increase in plasma glucagon like peptide-1 (GLP-1) levels enabled by cyclic adenosine monophosphate (cAMP)-independent pathway GPR40/120, as these GLP-1 release aids in insulin release, which further prove beneficial in reducing glucose level (Rivera-Mancía et al., 2018). Furthermore Yu and co-workers reported that curcumin (100 and 200 mg/kg/bw) in STZ induced diabetic rats reduced myocardial dysfunction, AGEs accumulation, cardiac fibrosis, inflammation, and ROS (Yu et al., 2012). In another study, dietary curcumin when administered to HFD hamsters increased the levels of high density lipoprotein-cholesterol (HDL-C) and decreased the levels of total cholesterol (TC), homeostatic model of assessment for IR (HOMA-IR) index and triglyceride (TG) as compared to reference group (Jang et al., 2008).One of the studies explored the protective actions of curcumin on IR, oxidative stress, inflammation and in high fructose fed male Wistar rats at the molecular level. It was noted that treatment with curcumin reduced IR by diminishing IRS-1 serine phosphorylation and enhancing IRS-1 tyrosine phosphorylation. It also decreased HOMA-IR, hyperinsulinemia, glucose intolerance, TNF-$\alpha$ and downregulated the COX-2 protein expression, PKC theta (Maithilikarpagaselvi et al., 2016). In another study curcumin was reported to decrease muscular IR by enhancing fatty acid and glucose oxidation when administered in HFD-STZ induced rats at a dose of 30 mg/kg/bw for 7 weeks (Na et al., 2011). In another study BGL was reported to reduce from 350 (mg/dl) to 100 (mg/dl) with treatment of nano curcumin in diabetic rats (Javidi et al., 2019). In another study curcumin reversed diabetic nephropathy in STZ-induced diabetic rats by inhibition of PKC$\beta$/p66Shc axis and activation of FOXO-3a (Altamimi et al., 2021). Moreover, administration of curcumin NPs in diabetic rats reduced hepatic inflammation, alleviated the reduced phosphorylation of AKT pathway, and counteracted diabetes-induced oxidative stress and inflammation in the internal hepatic and pancreatic tissues (Abdulmalek et al., 2021)

Besides animal studies, many clinical trials for curcumin in diabetic patients have also been reported. A randomized double blind controlled clinical trial treatment with curcumin capsules (Dose of 500 mg/day for 12 weeks), was reported to reduce TG/HDL-C ratio HOMA-IR and improved glycaemic status and lipid profile (Tamaddoni et al., 2019). In another clinical trial conducted in 60 women curcumin administration for 6 weeks at a dose of 500 mg/kg was reported to improve serum insulin and Quantitative Insulin Sensitivity Check Index (QUICKI) significantly and HOMA-IR slightly (Sohaei et al., 2019). Furthermore, in a placebo control trial involving 50 obese individuals curcuminoids administration (Dose of 300/mg/day)/3 months significantly reduced FBG, HbA1c, total fatty acids, TG and HOMA index (Rivera-Mancía et al., 2018). However, in another randomized trial no significant effect on BGL and lipid profile was seen in patients with DN when treated with encapsulated powdered turmeric rhizomes (1500 mg/day) for 2 months (Rivera-Mancía et al., 2018). Similarly administration of 98 mg of curcuminoids with increased bioavailability for 6 weeks with each principal meal served to attain curcuminoid build up in the blood, and was safe but had no effect on inflammation, iron homeostasis blood lipids and glucose, in hyperlipidemic individuals (Kocher et al., 2016). In another human trial the authors have found that curcumin capsules (475 mg) have significant effect in decreasing BGL, low density lipoprotein (LDL), TG, very LDL (VLDL), and increasing HDL in patients on glyburide therapy (Neerati et al., 2014). The authors have also reported that curcumin is a very useful supplement in T2DM patients who are on glyburide therapy, because of its permeability glycoprotein (P-gp) inhibitory actions, leading to enhancement of glyburide bioavailability (Neerati et al., 2014). In another clinical trial, treatment with combination of metformin and turmeric powder exhibited reduction in

**Table 1**
Molecular mechanism of curcumin for treatment of various disorders.

| S.No. | Disease | Molecular pathway | Reference |
|---|---|---|---|
| 1. | DM | • Reduction of oxidative stress and IR<br>• Deactivation of MAPK/JNK pathway; thus, reducing oxidative stress and improving insulin signaling<br>• Activation of AMPK which further activates P13K/Akt/mTOR which is responsible for cell survival and enhancement of antioxidant enzymes. It is responsible for transport of glucose inside cells<br>• Downregulation of NF-$\kappa\beta$ which reduces the pro-inflammatory cytokines | (Rivera-Mancía et al., 2018) |
| Diabetic complications | | | |
| 1.1 | DNP | • Reduction of oxidative stress and inflammatory markers<br>• Activation of Nrf2 and PPAR-gamma which further reduces oxidative stress<br>• Downregulation of NF-$\kappa\beta$ chemokines and protein kinases | (Soetikno et al., 2013b) |
| 1.2 | . . . | • Inhibits VEGF expression; thus, reducing vasopermeability and endothelial cell proliferation<br>• Reduction of AGEs which reduces oxidative stress<br>• Downregulation of NF-$\kappa\beta$ | (Mrudula et al., 2007) |
| 1.3 | DCP | • Activation of PKC, JNK, Nrf2 and PPAR-gamma<br>• Inhibition of TLR-4-MAPK/ NF-$\kappa\beta$ pathways and hence reduces the production of inflammatory cytokines and oxidative stress<br>• Improves dyslipidaemia | (Karuppagounder et al., 2017) |
| 1.4 | DN | • Suppression of JAK2-STAT3 pathway and NALP1 inflammasome which further downregulates IL-1$\beta$<br>• Reduction of AGEs<br>• Downregulation of NF-$\kappa\beta$ and MAPK/JNK pathway | (Liu et al., 2016) |
| 1.5 | DFU | • Inhibition of COX-2 and reduction of ROS<br>• Improvement in mitochondrial dysfunction and PKC inhibition<br>• Reduction of eNOS and iNOS levels<br>• Inhibition of MAPK/ NF-$\kappa\beta$ pathways | (Karri et al., 2015) |
| 2 | Neurodegenerative disorders | | |
| 2.1 | AD | • Reduction of neuronal loss by quenching ROS and reducing activated microglial cells<br>• Reduction of inflammation via inhibition of NF-$\kappa\beta$ and apolipoprotein E<br>• Maintenance of calcium levels | (Noguchi-Shinohara et al., 2019) |
| 2.2 | PD | • Downregulation of NF-$\kappa\beta$, VEGF, and TNF-$\alpha$,<br>• Reduction of inflammatory cytokine IL-1$\beta$, and IL-6,<br>• Downregulation of MAPK, Akt, COX-2, and 5-LOX) | (Farooqui 2019) |
| 3. | Cancer | • Downregulation of oncogenic miRNAs thus resulting in inhibition of carcinogenesis and metastasis<br>• Downregulation of PI3K/Akt, JAK/STAT, NF-$\kappa\beta$ and MAPK pathways which increase cell apoptosis<br>• inactivation of the Wnt/$\beta$-catenin signaling<br>• Activation of p53 signaling pathway thus preventing cancer cell proliferation | (Wang et al., 2019a) |
| 4. | CVDs | | |
| 4.1 | Aortic aneurysm | • Downregulation of NF-$\kappa\beta$ and JNK pathway<br>• Downregulation of AP-1 | (Li et al., 2020b) |
| 4.2 | Atherosclerosis | • Downregulation of TLR-4 which further inhibits NF-$\kappa\beta$ pathway and thus reduces pro inflammatory cytokines<br>• Inhibition of VCAM-1, ICAM-1 and TNF-$\alpha$<br>• Reduction of LPS which further improves intestinal barrier function<br>• Reduction of hyperlipidemia | |
| 4.3 | Cardiac hypertrophy and heart failure | • Inhibition of transcriptional co-activator p300 which reduces cardiomyocytes (overexpression of cardiomyocytes results in heart attack)<br>• Normalization of calcium levels<br>• Inhibition of (mTOR)/autophagy signaling pathway which reduces cardiac fibrosis | |
| 4.4 | MI | • Downregulation of PI3K/Akt, GSK-3$\beta$ and MAPK<br>• Downregulating EGR-1 and inflammatory factors such as TNF-$\alpha$, IL-6, P-selectin and ICAM-1<br>• Inhibition of JAK2/STAT3 | |
| 4.5 | Stroke | • Increased endothelial and mitochondrial function<br>• Downregulation of NF-$\kappa\beta$ | |
| 5. | Inflammatory disorders (RA and OA) | • Inhibition of NF-$\kappa\beta$, AP-1, Akt and JNK<br>• Upregulation of PPAR-gamma | (Wang et al., 2019b) |

DM: Diabetes mellitus; DNP: Diabetic nephropathy; DR.... . .: Diabetic retinopathy; DCP: Diabetic cardiomyopathy; DN: Diabetic neuropathy; DFU: Diabetic foot ulcer; AD: Alzheimer's disease; PD: Parkinson's disease; MI: Myocardial Infarction; OA: Osteoarthritis; IR: Insulin resistance; MAPK/JNK: Mitogen activated protein kinase/c-jun N-terminal kinases; 5′ adenosine monophosphate-activated protein kinase; P13K/Akt/mTOR: phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin; NF-$\kappa\beta$: Nuclear factor kappa beta; Nrf2: nuclear factor erythroid 2-related factor 2; PPAR-gamma; Peroxisome proliferator-activated receptor gamma; VEGF: Vascular endothelial growth factor; AGEs: Advanced glycation end products; PKC: Protein kinase c; TLR-4: Toll like receptor-4; JAK2-STAT3: Janus kinases2- signal transducer and activator of transcription proteins; NALP1: NAcht Leucine rich repeat protein-1; IL-1$\beta$: Interleukin-1$\beta$; ROS: Reactive oxygen species; eNOS: Endothelial nitric oxide synthase; iNOS: Inducible nitric oxide synthase; LOX: Lipo-oxygenase; AP-1: Activator protein-1; VCAM-1: Vascular cell adhesion molecule-1; ICAM-1: Intercellular adhesion molecule-1; LPS: Lipopolysaccharide; GSK-3$\beta$: Glycogen synthase kinase 3 beta; EGR-1: Early growth response-1.

FBG, glycated haemoglobin (HbA1c), LDL-C, non-HDL-C; inflammatory markers, and malondialdehyde (MDA) levels, and increased in total antioxidant status (Maithili Karpaga Selvi et al., 2015). Table 3 presents some other clinical studies of curcumin in treatment of DM and other disorders.

### 2.2. Inflammation

The root factor playing a role in different diseases such as cancer, DM, CVDs, inflammatory bowel disorders (IBD) is inflammation and curcumin acts as an anti-inflammatory drug to reduce inflammation

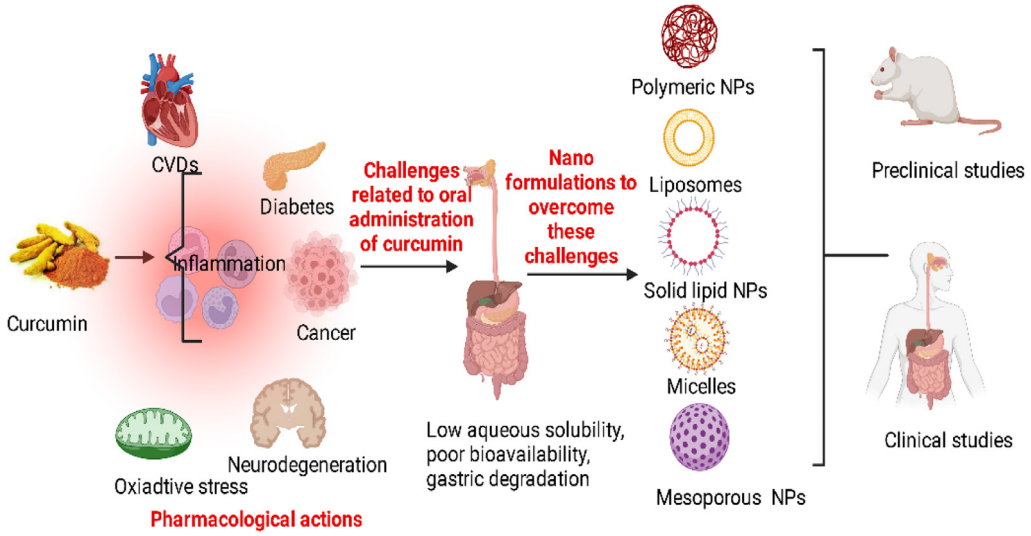


**Fig 1.** Pharmacological activities of curcumin and techniques to overcome its low solubility.

and prevent against these diseases. Inflammation is the body's natural protective response against pathogens or irritants. During inflammatory response immune cells release proinflammatory cytokines (TNF-$\alpha$ and interleukins) which act on endothelial cells and fibroblasts and increase coagulation and vascular permeability of cells. Excessive synthesis of these pro-inflammatory cytokines leads to inflammatory disorders. Curcumin plays an important role in reducing pro-inflammatory cytokine via different mechanisms (Salehi et al., 2019).

Many animal and human studies have explored the role of curcumin in different diseases involving inflammation. The first clinical research was conducted by Deodhar et al. in 2013 in which it was found that curcumin and phenylbutazone exhibited almost similar positive effects on walking time, muscle stiffness and swelling of joints of arthritic individuals, but had no effect on grip strength, ESR and joint index (Dcodhar et al., 2013). In another study curcumin analog A13 could reduce brain injury in diabetic rats by reduction of inflammation and oxidative stress (Miao et al., 2021).

Curcumin-enriched yoghurt exhibited anti-inflammatory and effective antioxidant activities (enhanced antioxidant enzyme actions and reduced lipid peroxidation) in kidney and liver of HFD mice (Costa et al., 2020). However, when given in combination with trigonelline, which is also a powerful antioxidant and anti-inflammatory molecule, these useful activities were nullified (Costa et al., 2020). In another study it was seen that curcumin could decrease acute pancreatitis via anti-oxidant, anti-apoptosis and anti-inflammation property resulting in decreased pancreatic damage (Siriviriyakul et al., 2019). In a recent study the authors have reported that curcumin exerted protective effects against hepatic chronic inflammation induced by bile duct obstruction in mice possibly via upregulating HO-1, thus can be helpful in mitigating chronic cholestatic liver diseases (Chen et al., 2020a). The results of another study revealed that pretreatment with curcumin for 30 days and/or rutin prevented the inflammation induced by hyperlipidemia in Wistar rats (Manzoni et al., 2019). Furthermore curcumin and allopurinol given to Wistar rats for 12 weeks remarkably increased the expression of miR-200a, consequently, reduced thioredoxin-interacting protein (TXNIP) and repressed NLRP3 inflammasome stimulation in liver of rat and thus revealed a hepatoprotective effect (Ding et al., 2018). Zhang et al. (Zhang et al., 2019a) explored the synergistic actions of curcumin and luteolin in human vascular cells and mice. Constantly, curcumin and luteolin given in combination at a dose of 500 mg/kg each for 2 weeks synergistically reduced adhesion of monocytes to aortic endothelium triggered by TNF-$\alpha$- in mice. Moreover the expression of VCAM-1 and MCP-1 was also increased by TNF-$\alpha$ through inhibition of NF-$\kappa$B transportation inside the cells. Furthermore, the effect of curcumin in colistin-induced neurotoxicity and nephrotoxicity confirmed that curcumin alleviated oxidative damage, inflammation and apoptosis in Albino rats. The increased levels of NO, IL-6, MDA TNF-$\alpha$, and caspase-3 expression levels were significantly reversed after curcumin administration at a dose of 200 mg (Edrees et al., 2018). In a clinical study conducted in T2DM patients, oral intake of curcumin exhibited a noteworthy enhancement in endothelial function, MDA, IL-6, and TNF-$\alpha$ levels. Satoskar et al. compared the effect of curcumin with phenylbutazone or placebo for its anti-inflammatory properties in postoperative patients wherein curcumin significantly showed a reduction in inflammation and cytokines such as TNF-$\alpha$ and IL-6 (Salehi et al., 2019).

Curcumin has shown potential effects in treating RA and OA. RA is an autoimmune inflammatory disorder affecting the joints and resulting in painful swelling, pannus formation, bone erosion, hyperplasia and joint deformity. The pathogenesis of RA mainly involves B cells, T cells and the orchestrated interaction of pro-inflammatory cytokines such as TNF-$\alpha$, IL-6 and IL-1. Moreover Fibroblast-like synoviocytes (FLS) generate many proinflammatory factors, chemokines MMPs, and cathepsin which result in the bone extracellular matrix and cartilage degradation. Curcumin inhibits abnormal hyperplasia, inflammatory cytokines, and matrix metalloproteinases via regulation of different pathways such as mTOR NF$-\kappa$B and NLRP3 inflammasome signaling (Dai et al., 2018).

OA is another inflammatory disease wherein there is loss of chondrocytes and cartilage destruction in joints. The pathogenesis involves release of cytokines and inflammatory mediators that further produce NO, resulting in chondrocyte apoptosis and ECM degeneration. These cytokines activate matrix metalloproteinase (MMPs) which digest both macromolecules of the ECM and the ones which are not located in ECM, such as receptors, growth factors, cytokines, and chemokines. Curcumin, alters the inflammatory response by inhibiting COX-2, LOX, and increasing iNOS. Curcumin inhibits the release of inflammatory cytokines, and MCP and reduces the regulation of mitogenic activation and JAK (Nicoliche et al., 2020).

Moreover, curcumin also shows potential effects in treating various colonic diseases such as ulcerative colitis (UC) and chrons disorder. It has been found that curcumin treats colonic diseases by decreasing ROS and inflammatory cytokine production, and by suppression of neutrophils iNOS migration in the intestine (Arafa et al., 2009).

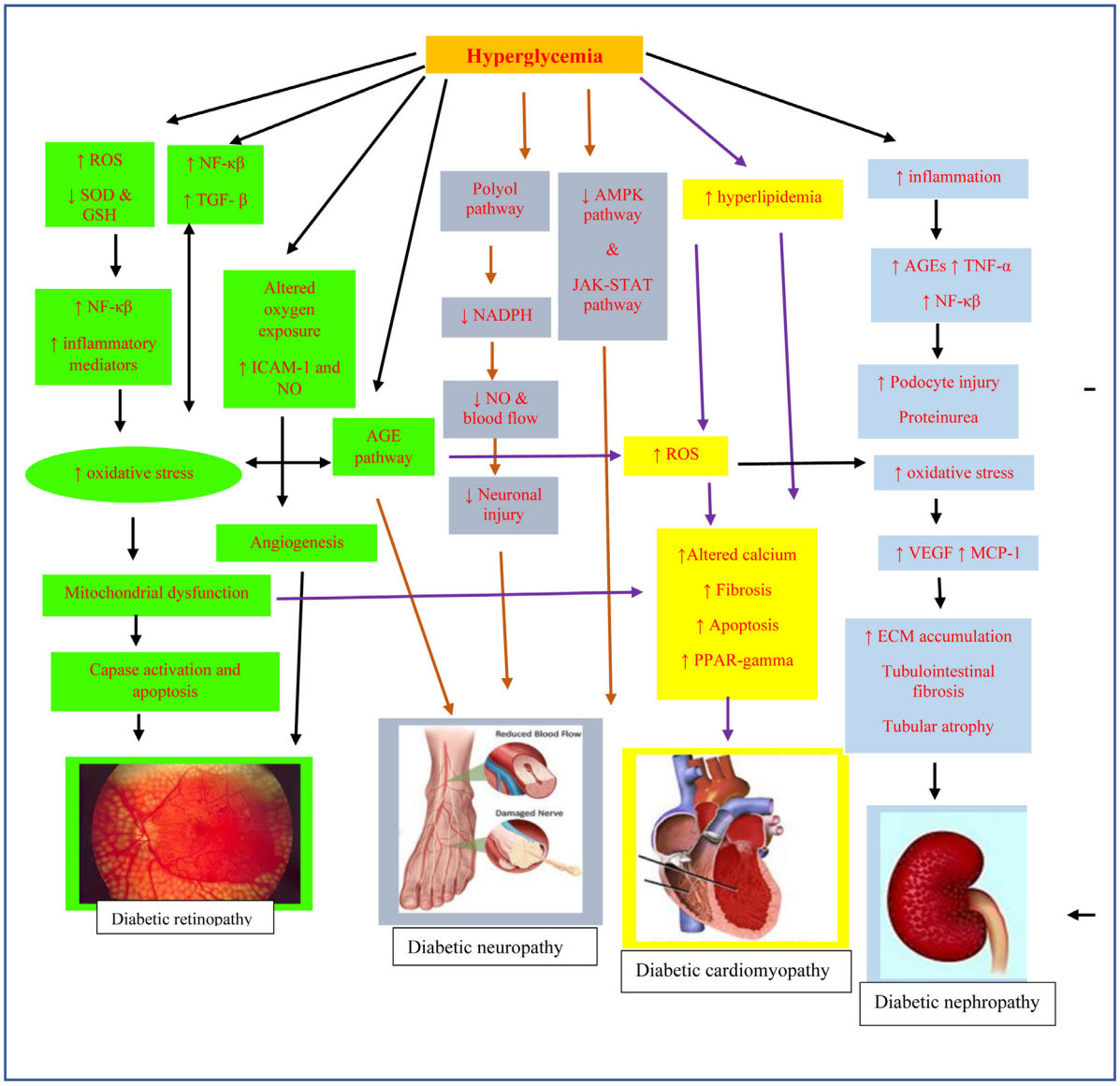


**Fig 2.** Pathogenesis involved in the development of diabetic complications

↑: Increase; ↓: Decrease; ROS: Reactive oxygen species; SOD: Superoxide dismutase; GSH: Glutathione; TGF- $\beta$: Transforming growth factor beta; NF-$\kappa\beta$: Nuclear factor kappa beta; ICAM 1: Intercellular adhesion molecule 1; NO: Nitric oxide; NADPH: Nicotinamide adenine dinucleotide phosphate; 5′adenosine monophosphate protein kinase; JAK-STAT: Janus kinase-signal transducer and activator of transcription proteins; AGEs: Advanced glycation end products; TNF-$\alpha$: Tumor necrosis factor alpha; VEGF: Vascular endothelial growth factor; MCP-1: Monocyte chemoattractant protein-1; ECM: Extracellular matrix.

### 2.3. CVDs

**CVD is a general condition in which the blood vessels and heart are affected.** It's usually linked with a deposition of fats and lipids inside the arteries and an increased risk of blood clots. The major CVDs include aortic aneurysm, atherosclerosis, heart failure, cardiomyopathy, MI and stroke. Numerous studies have shown the potential effect of curcumin in treating CVDs. Curcumin supplementation (100 mg/kg/day, for 14 days) decreased the enhancement in aortic diameter, and repressed expression of pro-inflammatory enzymes by obstructing NF-$\kappa$B activation (Parodi et al., 2006). In another research curcumin at the same dose beneficially improved growth of the thoracic aortic diameter induced by $CaCl_2$ and conserved elastin fibers in rats (Fan et al., 2012). Similar dose of curcumin in another study reduced aortic aneurysm progression, infiltration of macrophages and the generation of pro-inflammatory cytokines. Moreover the levels of SOD was enhanced and extracellular signal-regulated kinase (ERK) pathway was inhibited. Li et al., demonstrated that curcumin administration decreased the size of thoracic aortic aneurysm and also reduced the VEGF synthesis in rats (Li et al., 2017). It has been demonstrated that curcumin shows antihyperlipidemic activities by reducing oxidized LDL deposition, which in combination with its anti-inflammatory and anti-oxidant activity, can diminish the frequency of atherosclerosis (Li et al., 2020a). Furthermore curcumin decreased atherosclerotic lesions and inhibited the pro-inflammatory mediator expression in macrophages isolated from the spleen of $ApoE^{-/-}$ mouse model when given at a dose of 200 mg/kg/bw (Guo et al., 2018). Zhao et al. described protective actions in mice supplemented with curcumin (20 mg/kg/day) for 4 weeks against the progression of atherosclerosis (Zhao et al., 2012). In another study curcumin reduced the build-up of cholesterol in the growth of foam cells. The increase in uptake of lipids and decreased efflux of cholesterol was important in growth of foam cells (Tian et al., 2019). Further research showed the fine-tuned effects of curcumin on cholesterol in macrophages. The anti-atherogenic activities were projected to be arbitrated by inhibition of scavenger receptors through activation of

**Table 2**
Preclinical studies of curcumin in treatment of different diseases.

| S.N | Disease | Animal | Dose (mg/kg) | Duration of treatment | Results | Reference |
|---|---|---|---|---|---|---|
| Diabetic complications | | | | | | |
| 1. | … | Rats | 100 | 16 weeks | Reduced BGL, retina thinning, GC death and possessed strong antioxidant activity in retinaEnhanced Bcl-2 expression and reduced Bax in the retina | (Yang et al., 2018a) |
| 2. | | SD rats | 100 | 12 weeks | Reduced retinal vascular leakage improved blood vessel density improved GC in retinaReduced iNOS, VEGF, and ICAM-1 expressions and supressed NF-kB pathway | (Pradhan et al., 2018) |
| 3. | | SD Rats | 100 | 12 weeks | Inhibited glucose induced CaMKII and NF-$\kappa$B pathways and decreased iNOS, ICAM-1 and VEGF | (Li et al., 2016) |
| 4. | | Rats | 1000 | 16 weeks | Reduced inflammatory cytokines and ROSReduced VEGF and prevented structural degeneration in retina | (Aldebasi et al., 2013) |
| 5. | | SD rats | 100 | 12 weeks | Inhibited neuronal loss of retina by inhibiting CaMKII and reducing glutamate level | (Li et al., 2015) |
| 6. | DN | SD rats | 200 | 14 days | Inhibited neuropathic pain by reducing oxidative stress via inhibition of NADPH oxidase | (Zhao et al., 2014) |
| 7. | | SD rats | 200 | 21 days | Reduced nerve conduction velocity and pain | (Nagilla and Reddy 2014) |
| 8. | | SD rats | 60 | 28 days | Reduced pain hypersensitivity, allodynia, hyperalgesia and TNF-$\alpha$ levels | (Li et al., 2013) |
| 9. | DNP | SD rats | 300 | 8 weeks | Reduced serum creatinine, urine albumen and urea nitrogenEnhanced E-cadherin and LC3 proteins expressionReduced p62, phosphorylated levels of Akt and mTOR, and P13K levels | (Tu et al., 2019) |
| 10. | | db/db mice | 200 | 16 weeks | Reduced renal hypertrophy and reduced NLRP3 protein and IL-1$\beta$Inhibited collagen IV and fibronectin protein expressions | (Lu et al., 2017) |
| 11. | | OLETF rats | 100 | 45 weeks | Reduced albuminuria, urinary MDA and SOD via Nrf2 signaling,Reduced ectopic lipid deposition by upregulation of AMPK signaling. | (Kim et al., 2016) |
| 12. | | SD rats | 100 | 8 weeks | Increased AMPK phosphorylation and reduced renal expression of SREBP-1cReduced plasma and renal TGReduced the TGF $\beta$ and VEGF | (Soetikno et al., 2013a) |
| 13. | | SD rats | 100 | 8 weeks | Reduced TGF$-\beta$1, CTGF, osteopontin, p300 and ECM proteinsReduced VEGF expressionReduced lipid peroxidation, NOX4 and increase antioxidant enzymes | (Soetikno et al., 2011) |
| 14. | DCP | Wistar rats | 100 | 6 weeks | Regenerated myocardium and reduced Creatine Kinase-MB and TGF-$\beta$1 levelsReduced lipid peroxidation, IL-6, and NF-$\kappa$BActivated JAK/STAT pathway and suppressed Nrf2/HO-1 pathway | (Abdelsamia et al., 2019) |
| 15. | | SD rats | 300 | 16 weeks | Suppressed collaged synthesis due to increased BGLInhibited TGF-$\beta$1 production and blocked AMPK/p38 MAPK pathway | (Guo et al., 2018) |
| 16.. | | Wistar rats | 100 | 16 weeks | increased anti-apoptosis protein (Bcl-2) and decreased pro-apoptosis protein (Bax) expression | (Zhou and Zhang 2017) |
| 17. | | Wistar rats | 200 | 6 weeks | Reduced BGL, TG, TC, NO, cardiac MDA, inflammatory cytokines, and increased cardiac antioxidant enzymes (CAT, SOD, and GST). | (Abo-Salem et al., 2014) |
| Inflammatory disorders | | | | | | |
| 18. | RA | Wistar rats | 200 mg/kg | 3 weeks | Reduced hyperplasia and inflammation via mTOR pathwayIL-1$\beta$, TNF-$\alpha$, MMP-1, and MMP-3 | (Dai et al., 2018) |
| 19. | | Mice | 50 mg/kg | 28 days | Suppressed IFN$\gamma$-induced BAFF expression, IL-6 production and nuclear translocation | (Huang et al., 2013a) |
| 20. | | SD rats | 110 mg/kg | 2 weeks | Reduced pannus formation and cartilage erosion | (Kamarudin et al., 2012) |
| 21. | OA | Wistar | 50 mg/kg | 60 days | Reduced cartilage injury and increased chondrocytes | (Nicoliche et al., 2020) |
| 22. | | Wistar rats | 500 mg/kg | 5 weeks | Reduced nitro tyrosine, TNF-$\alpha$, phosphorylated NF-$\kappa\beta$, and cleaved caspase-3 | (Park et al., 2020) |
| 23. | | SD rats | 200 mg/kg | 2 weeks | Reduced inflammation by downregulation of TNF$-\alpha$, IL$-1\beta$, and IL6Blocked TLR4 /MyD88/NF$-\kappa$B signal pathway | (Zhang and Zeng 2019) |
| 24. | UC | Mice | 80 mg/kg | 7 days | Reduction of proinflammatory cytokine production and disruption of colonic architectureUpregulated mTOR and SIRT1 pathways | (Zhang et al., 2019b) |
| 25. | | Mice | 0.1 mmol/kg | 7 days | Reduced colitis induced injury via downregulation of NF-$\kappa$B/STAT3 and reduction of COX-2 and iNOS expression | (Yang et al., 2018b) |
| 26. | | Swiss Albino rats | 100 mg/kg | 7 days | Regulated oxidant/anti-oxidant balance and reduced the release of TNF-$\alpha$ and NOReduced MDA and lipid peroxidation | (Arafa et al., 2009) |
| 27. | | Mice | 100 mg/kg | 7 days | Reduced colonic mucosal damage via downregulation of JAK/STAT/SOCS signalingReduced pro inflammatory cytokines (IL-12, IL-15, and IL-23), and enhanced IL-4, IL-10, and IFN-$\gamma$ levels | (Zhao et al., 2016) |
| 28. | Hepatic inflammation | SD rats | 30 and 60 mg/kg | 6 weeks | Reduced inflammation via up-regulating miR-200a-mediated TXNIP/NLRP3 inflammasome pathway | (Ding et al., 2018) |
| CVDs | | | | | | |
| 29. | Stroke | C57BL/6 mice | 100 200 and 300 mg/kg | | Decreased infarct volume and neuronal damage, enhanced neurological function | (Xie et al., 2018) |
| 30. | | Albino Wistar | 25 mg/kg | | Reduced brain edema and water contentReduced pro-inflammatory cytokinesReduced mitochondrial membrane potential | (Zhang et al., 2017) |
| 31. | Atherosclerosis | Mice | 0.1% w/w | 16 weeks | Reduced atherosclerotic lesions by 45%Reduced TC and LDL-CReduced deposition of cholesterol in the aortas by 56%D | (Zou et al., 2018) |

(*continued on next page*)

**Table 2** (*Continued*)

| S.N | Disease | Animal | Dose (mg/kg) | Duration of treatment | Results | Reference |
|---|---|---|---|---|---|---|
| 32. | | LDLR$^{-/-}$ mice | 100 mg/kg | 18 weeks | Reduced atherosclerotic lesions, VCAM−1 and ICAM−1 localization, lipid infiltrationReduced plasma cholesterol, TGs, LDL-C and Apo B levels Increased plasma HDL-C and liver Apo A−I expression | (Shin et al., 2011) |
| 33. | | Mice | | 8 weeks | Decreased IL-4 and IL-13 in serumReduced inflammatory factors IL-6, iNOS and IL-1$\beta$ | (Gao et al., 2019) |
| 34. | Aortic aneurism | Rats | 100 mg/kg | 4 weeks | Decreased aneurysm sizeRestored the wavy structure of the elastic lamellae.Reduced neovascularization and VEGF expression | (Li et al., 2017) |
| 35. | Cardiac hypertrophy | Wistar rats | 50 mg/kg | 10 weeks | Increased the survival rate and decreased the ratio of heart or left ventricle to body weightUpregulated myocardial NCX and eNOS levels | (Bai et al., 2018) |
| 36. | MI | C57BL/6 J mice | | 4 weeks | Reduced collagen depositionInhibited MMP expression and cardiac fibroblast proliferation and migration, | (Xiao et al., 2016) |
| 37. | | SD rats | 150 mg/kg | 4 weeks | Increased cell survival, Reduced fibrous tissue proliferation and infiltration of inflammatory cellsInhibited NF-$\kappa$B expressionIncreased PPAR-$\gamma$ expression | (Lv et al., 2016) |
| 38. | Chronic heart failure | New Zealand rabbits | 100 mg/kg | 10 weeks | Reduced myocardial fibrosisUpregulated MMP-2 and MMP-9 expressionattenuated left ventricular dysfunction | (Tang et al., 2009) |
| 38. | Myocardial fibrosis | SD rats | 150 mg/kg | 4 weeks | Reduced macrophages and smooth muscle actin-expressing myofibroblasts, Inhibited collagen I synthesis was inhibitedAttenuated tissue fibrosis | (Pang et al., 2015) |
| 39. | | SD rats | 200 mg/kg | 4 weeks | Attenuated cardiac hypertrophy via targeting of mTOR/autophagy axis | (Liu et al., 2018a) |
| Neurodegenerative disorders | | | | | | |
| 40. | AD | SD rats | 8 mg/kg | 4 weeks | Ameliorated the altered insulin signaling | (Das et al., 2019) |
| 41. | | Wistar rats | 50 and 100 mg/kg | 1 month | Reduced recognition memory deficitsImproved neuroinflammation | (Bassani et al., 2017) |
| 42. | | C57BL/6 transgenic APP/PS1 mice | 150mg | 42 days | Enhancement of memory and learning functionIncreased new neural stem cells (BrdU$^{+}$/Nestin$^{+}$) and newborn neurons (NeuN/kI67$^{+}$) in the hippocampal regionAmeliorated cognitive impairment | (Li et al., 2019a) |
| 43. | | SD rats | 300 mg/kg | 7 days | Relieved spatial learning and memory deficits,Reduced hippocampus neuronal apoptosis,Decreased JNK-3 and p-JNK-3 levels | (Wang et al., 2017b) |
| 44. | | Kunming mice | 10 mg/kg | 14 days | Reduced A$\beta$ productionReduced IL-1$\beta$, IL-6 and TNF-$\alpha$ levelsImproved learning and memory function | (Liu et al., 2018b) |
| 45. | | Rats | 300 mg/kg | 6 days | Exhibited remarkable improvement in the spontaneous alternation in Y-maze and memory ability in the water maze test | (Geng et al., 2016) |
| 46. | PD | Swiss albino mice | 80 mg/kg | 12 days | Decreased the $\alpha$-synuclein levelsIncreased the Dopamine and serotonin levelsDecreased MDA, GSH and SODDecreased inflammatory markers Ang-II, CRP and IL-6 levels | (Motawi et al., 2020) |
| 47. | | Wistar rats | 5 10 and 20 mg/kg | 45 days | Reduced neurochemical deficits, motor dysfunctions, and oxidative stress and Reduced inflammatory markers | (Ramkumar et al., 2018) |
| 48. | | Wistar Albino rats | 200 mg/kg | 3 weeks | Improved the electrophysiological parametersReduced motor impairments | (Darbinyan et al., 2017) |
| 49. | | Mice | 50 100 and 200 mg/kg | 3 weeks | Improved behavioural alterations,Reduced oxidative damage and acetylcholine esterase enzyme levelRestored motor deficits | (Khatri and Juvekar 2016) |

IFN$\gamma$: Interferon gamma; BAFF: Bcell activating factor; MyD88: Myeloid differentiation primary response protein; Ang-II: Angiotensin- II; SIRT1: Sirutin 1; NCX: Sodium calcium exchanger in neurons.
SD: Sprague Dawley; GC: Ganglionic cell; BCL-2: B-cell lymphoma-2; Bax: Bcl-2 associated X protein; CaMKII: Calcium/calmodulin dependent protein kinase II; NADPH: Nicotinamide adenine dinucleotide phosphate; SREBP-1c: Sterol regulatory element-binding protein 1; TGF−$\beta$1: Transforming growth factor beta 1; CTGF: Connective tissue growth factor; ECM: Extracellular matrix; NOX4: NADPH oxidase 4: NLRP3: Nucleotide-binding domain-like receptor protein 3: SOD: Superoxide dismutase; LC3: Light chainHO-1: Heme oxygenase 1; NO: Nitric oxide; GST: glutathione−S−transferase.

**Table 3**
Clinical studies of curcumin for treating different diseases.

| S.N | Disease | Trial | No of patients | Duration of treatment | Results | Reference |
|---|---|---|---|---|---|---|
| DM | | | | | | |
| 1. | DNP | R DB PC | 20 | 66.3 mg daily for 2 months | Reduced TGF-$\beta$ and IL-8 serum levelsDecreased urinary excretion of protein and IL-8 | (Khajehdehi et al., 2011) |
| 2. | DM | R DB PC | 16 | 180 mg for 12 weeks | Reduced IR and TGs | (Thota et al., 2019) |
| 3. | | R DB CO PC | 44 | 1500 mg for 10 weeks | Reduced inflammatory markers (TG, hsCRP, adiponectin) | (Adibian et al., 2019) |
| 4. | | R DB PC | 53 | 1500 mg for 10 weeks | Reduced body mass and FBG | (Hodaei et al., 2019) |
| 5. | | R DB PC | 50 | 500 mg for 3 months | Reduced HbA1c | (Panahi et al., 2018) |
| 6. | | R DB PC | 118 | 1000 mg for 8 weeks | Increased SOD and reduced MDA activity | (Panahi et al., 2017) |
| 7. | | PT R DB PC | 58 | 1000 mg/day for 8 weeks | Reduced BMI, BGL and HbA1cIncreased adiponectin and reduced leptin | (Panahi et al., 2016b) |
| Inflammatory diseases | | | | | | |
| 8. | RA | R DB PC | 12 | 250 and 500 mg/kg twice daily for 3 months | Improvement in the CRP, ESR, VAS, DAS28, and RF responses | (Amalraj et al., 2017) |
| 9. | OA | R DB PC | 19 | 1500 mg/kg for 6 weeks | Increased antioxidant activityIncreased SOD and GSH and reduced MDA activity | (Panahi et al., 2016a) |
| 10. | | R DB | 34 | 120 mg for 4 weeks | Inhibited COX-2 | (Kertia et al., 2012) |
| 11. | | R DB PC | 19 | 1500 mg for 6 weeks | Reduced TNF-$\alpha$ and TGF-$\beta$ | (Rahimnia et al., 2015) |
| 12. | | R DB PC | 201 | 1050 mg for 12 weeks | Reduced pain | (Haroyan et al., 2018) |
| 13. | NAFLD | R | 43 | 1000 mg for 8 weeks | Reduced TC, TGs, LDL-C and increased HDL-C | (Panahi et al., 2016d) |
| 14. | Inflammation | PHA | 59 | 1000 mg for 8 weeks | Reduced IL-6, TNF-$\alpha$, MCP-1 and TGF-$\beta$ | (Panahi et al., 2016b) |
| Cancer | | | | | | |
| 15. | Colorectal cancer | NR OL | 44 | 2 or 4 g for 1 month | Decreased aberrant crypt foci | (Carroll et al., 2011) |
| 16. | Solid tumor | R DB PC | 40 | 180 mg/d for 8 weeks | Reduced TNF−$\alpha$, TGF$\beta$, IL−6, substance P, hs−CRP and MCP−1 | (Panahi et al., 2014b) |
| 17. | Prostate cancer | | 20 | 3 g/d for 3 months | Improved antioxidant status (Increased SOD and reduced TAC) | (Hejazi et al., 2016) |
| CVDs | | | | | | |
| 18. | Coronary artery disease | R DB | 33 | 500 mg for 8 weeks | Reduced TG, LDL-C, VLDL-C | (Mirzabeigi et al., 2015) |
| 19. | Atherosclerosis | R DB PC | | 6 months | Decreased pulse wave velocity, increased serum adiponectin and reduced leptinDecreased uric acid, visceral fat, IR and TGs | (Panahi et al., 2016c) |
| 20. | | R DB | 50 | 1000 mg/d for 8 weeks | Reduced LDL-C, non-HDL-C, TC, TGs and increased HDL-C | (Panahi et al., 2014a) |
| 21. | | R DB PC | 30 | 1 g/day | Reduced TGs | (Mohammadi et al., 2013) |
| Neurodegenerative diseases | | | | | | |
| 22. | Depression | R DB PC | 123 | 500 and 1000 mg for 8 weeks | Decreased depressive and anxiolytic symptoms | (Lopresti and Drummond 2017) |
| 23. | AD | R DB PC | 36 | 2 and 4 g for 24 weeks | Unable to demonstrate clinical activity | (Ringman et al., 2012) |

R: Randomized; DB: Double blind; PC: Placebo controlled; PT: Pilot; CO: Crossover; PHA: Post hoc analysis; NR: Non randomized; BMI: Body mass index; hsCRP: High sensitivity c reactive protein; ESR: TAC: Total anti-oxidant capacity; MCP-1: Monocyte chemoattractant protein-1; ESR: Erythrocyte sedimentation rate; VAS: Visual analogue scale; DAS: Disease activity score; RF: Rheumatoid facto; NAFLD: Non alcoholic fatty liver disease.

proteasome and by enhancing ATP-binding cassette transporter (Zhao et al., 2012). Moreover, curcumin treatment for 16 weeks (100 mg/kg/day) in mice prevented atherosclerosis by reducing the level of LPS and improving the intestinal barrier function. In other study when curcumin was given to mice for 1 and a half year in diet, it reduced hyperlipidemia and atherosclerotic lesions (Li et al., 2020a). Curcumin also beneficially affects calcium-associated molecules and hence inhibited cardiac hypertrophy and heart failure. These effects include enhancing expression and altering localization of $Na^+/Ca^{2+}$ exchanger (Bai et al., 2018), stabilizing the $Ca^{2+}$ amount of sarcoplasmic reticulum (SR) (Shi et al., 2017), increasing protein expression of SR $Ca^{2+}$-ATPase (Zhang et al., 2010), and inhibiting CaMK II pathway (Ghosh et al., 2014). Current study revealed that curcumin suppressed signaling pathways of autophagy which result in a reduction of cardiac hypertrophy. Constantly, in Angiotensinogen II permeated rats curcumin treatment for 4 weeks decreased macrophage count and fibroblast migration, propagation and collagen synthesis at 150 mg/kg dose. Further work showed that these actions were due to reduction in phosphorylation of Smad2/3 and inhibition of ERK1/2 pathway. Moreover, increased gelatinase MMP-2 and MMP-9 activity as well as expression were also attributed towards the defensive actions of curcumin against chronic heart failure (Li et al., 2020a). Benzer et al. stated that curcumin enhanced the activity of antioxidants and reduced inflammation and hence protected against cardiotoxicity induced by doxorubicin. (Benzer et al., 2018). Many drugs such as cisplatin, methotrexate and doxorubicin have results in cardiotoxicity; and curcumin administration in such cases effectively reduced the oxidative stress and hence ameliorated the cardiac damage (Bahadır et al., 2018; Chakraborty et al., 2017; Ciftci et al., 2018). In another study synergistic effect of curcumin and miR-144-3p was obtained in treating myocardial infarction (Kang et al., 2021). In another study, Hong et al. confirmed that curcumin administration at a dose of 75 mg/kg/day prominently improved cardiac functions and also decreased the size of cardiac necrosis in comparison to reference group (Li et al., 2020a).

Certain clinical trials of curcumin have also shown its beneficial effects. For example, in a controlled trial, a total of 118 T2DM individuals were randomized for curcumin administration for 12 weeks.

**Table 4**
Cell line studies using various drug delivery systems of curcumin.

| S.N | Formulation | Type of cancer | Cell line | Result | Reference |
|---|---|---|---|---|---|
| 1. | Eloctrospun nanofiber | Breast cancer | T47D | 10:5% curcumin-chrysin-nanofibers revealed the best synergistic cytotoxicity against the cells. | (Rasouli et al., 2020) |
| 2. | Flower-like curcumin-loaded folic acid-conjugated ZnO-MPA- $\beta$cyclodextrin nanostructures | Breast cancer | MDA-MB-231 | The formulation exhibited larger selective apoptosis-induced anticancer activity in cell lines. Conjugation with folic acid improved cellular uptake of curcumin in cell lines. | (Ghaffari et al., 2019) |
| 3. | Gemini–Curcumin polymersomes | Breast cancer | T47D | This nano formulation suppressed cancer cell propagation via induction of apoptosis and upregulated the expression of p14ARF, p16INK4a and Bax, while prominently reduced the Bcl-2 expression in these breast cancer cells. | (Karimpour et al., 2019) |
| 4. | Fungal chitosan NPs | Colon cancer | HCT-116 and A-549 | Treatment with the formulation lead to time-dependent decrease of cell survival; the dead cells were 67.6% from HCT-116 and 73.8% from A-546 after 96 h. | (Almutairi et al., 2019) |
| 5. | Citrus pectin chitosan NPs | Colon cancer | | The formulation presented maximum mucoadhesion tendency in the large intestinal media and least at pH 1.2 (stomach). At pH 1.2 18% drug release was obtained in 2 h whereas 68% in the caecal medium in 24 h. | (Sabra et al., 2018) |
| 6. | Pickering emulsion | Fibroblast and breast cancer | L929 and MCF-7 | The emulsion prevented microbial growth and inhibited exclusive killing of cancer cells in comparison to normal cells. | (Asabuwa Ngwabebhoh et al., 2018) |
| 7. | Zinc oxide NPs | Breast cancer | MDA-MB-231 | MTT cytotoxicity evaluation on cell lines showed a reduction in IC50 leading to increased cancer-inhibitory activity | (Ghaffari et al., 2017) |
| 8. | Mucoadhesive NPs | Colon cancer | Colorectal cells | Mucoadhesive NPs led to a greater decrease in percentage cell viability as well as a lower IC50.The formulation as well as free curcumin induced cell death in colorectal cancer cells, by arresting the cell cycle at G2/M stage. | (Chuah et al., 2014) |
| 9. | Chitosan NPs | Colon cancer | HT29 | 2.5 to 3 fold enhancement of anticancer activity | (Anitha et al., 2014a) |
| 10. | Chitosan NPs | Colon cancer | HT29 | Sustained release profile of curcumin was obtained over a period of 4 days profile in pH 4.5 and 7.4 with increased anticancer effects. | (Anitha et al., 2014b) |
| 11. | SNEDDS | Lung cancer | Adeno-carcinoma epithelial cell line | Increased bioavailability and reduced lung cancer | (Chopraa et al., 2011) |

Administration of curcumin lead to a reduction in cardiovascular risks complicated by dyslipidaemia (Panahi et al., 2016d). Furthermore in a study enrolling 10 male individuals, curcumin decreased the oxidative stress induced by exercise (Takahashi et al., 2014). Another study including 45 postmenopausal women showed that when curcumin was administered along with endurance exercise it potentially decreased the left ventricular afterload. The combination was also helpful in reducing the systolic blood pressure in these patients (Sugawara et al., 2012). Another randomized trial on 87 subjects for 8 weeks with non-alcoholic fatty liver diseases revealed a significant decrease in total cholesterol, non-HDL-C, and triglycerides mediated by curcumin supplementation (Panahi et al., 2016d). Curcumin (80 mg/day) was administered to 38 individuals to investigate curcumin effects in healthy subjects. It was found that curcumin prominently decreased the levels of triglyceride and some crucial parameters, such as salivary amylase and plasma beta amyloid protein (Panahi et al., 2016d). In another trial it was reported that curcumin treatment reduced the LDL and Apo B levels and improved Apo A levels. The lower ratio of Apo B-Apo A helps in treating the conditions of atherosclerosis (Ramırez-Boscá et al., 2000). In another placebo control study which was conducted for 12 weeks on 22 men, the researchers have found that curcumin improved homocysteine and HDL levels, which are the major factors responsible for maintenance of cardiovascular health in young and obese men (Campbell et al., 2019).

### 2.4. Anticancer effects

Curcumin has also been used for treatment of different types of cancer such as breast cancer, colon cancer and gastric cancer (Jakubek et al., 2019; Shabaninejad et al., 2020). Different formulations of curcumin have shown effects on cancer cell lines which are described in Table 4. Mitocurcumin which is a derivative of curcumin induced apoptosis of lung cancer cells through mitochondrial pathway and depleted lung cancer stem cells. This was because of modulation of thioredoxin reductase 2 (TrxR2) action to NADPH oxidase like activity by mitocurcumin, leading to enhanced ROS buildup and cell death (Jayakumar et al., 2017). Chen et al. (2020b) developed nano-micelles of curcumin which showed enhanced solubility than raw curcumin and also exhibited stronger anticancer and antioxidant actions than curcumin. In another study, authors reported that curcumin altered the membrane potential of breast cancer cells and thus induced cell death in maximum cell lines (Karunagaran et al., 2005). Zhou et al. used cisplatin and paclitaxel individually as well as in combination with curcumin to treat MCF-7 and MBA-MB-231 cell lines. The synthetic drugs reduced the rate of survival and curcumin reduced the IC50 of investigational cell lines (Zhou et al., 2015). In one of the studies it was reported that curcumin reduced the association of myeloid-derived inhibitor cells in malignant tissue (Tu et al., 2012). It was detected that stimulation and mobilization of myeloid derived suppressor cells (MDSCs) are serious initial steps for IL-1$\beta$-triggered stomach cancer (Tu et al., 2008). The potential analogue of curcumin i.e. curcumin W346, which had a low toxic effects in healthy intestinal mucosa and possessed increased stability, was synthesized and established by Xia et al. (2016) . The researchers revealed that curcumin potentially repressed propagation and incursion in stomach cancer cells expectedly due to reduction in NF-$\kappa$B stimulation (triggered by TNF-$\alpha$ and IL-1$\beta$) (Qiu et al., 2017). Likewise, Belcaro et al. claimed that co-application of curcumin strongly decreased the side effects in cancer patients in those who are on 5-fluorouracil chemotherapy for gastric cancer (Belcaro et al., 2014)

Perry and the co-authors have reported anti-carcinogenesis effects of curcumin in glioblastoma xenografts. Curcumin supplementation decreases MMP-9, gelatinolytic actions, and endothelial cell markers which is a sign of reduced angiogenesis. Furthermore, the controlled effects of curcumin on colony formation, proliferation, migration and tumor size have been assessed in glioma cell lines and mice model (Perry et al., 2010). Treatment with curcumin leads to

downregulation of SHH/GLI1 signaling (GLI1, Smo and Shh), CyclinD1, Bcl-2 and Foxm in vitro. It also enhances the Bax/Bcl2 ratio, thus inducing apoptosis in cancerous cells. Curcumin confines cancer cells and delays the survival period of U87-implanted nude mice in comparison to control subjects through SHH/GL1 signaling pathway. In another research nano CurcTM which is 50 nm in size was synthetized by encapsulation of curcumin in cross-linked and random copolymers of N-vinyl-2-pyrrolidone (VP), N-isopropylacrylamide (NIPAAM), and poly (ethyleneglycol) monoacrylate (PEG-A). In comparison to raw curcumin, it exhibited more solubility in aqueous medium. In addition, its anti-cancer actions on different human cancer cell lines and animal models of human malignancies were notable and tremendously promising (Du et al., 2013).

### 2.5. Neurodegenerative disorders

Neurodegenerative disorders are characterized by selective and symmetric neuronal loss in the sensory, motor, or cognitive systems. The common neurodegenerative disorders include Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (Martin 1999)

### 2.6. AD

AD has no identified cure, nor is there a clear mechanical understanding of the disease process itself. Although neurofibrillary tangles, amyloid plaques, and cognitive decline are late-stage markers of the disease, it is not clear how they are originally caused. It has been identified that noticeable dysregulations in calcium signaling and associated downstream pathways, occur before the cognitive or diagnostic histopathological alterations. Certainly, upon studying the current literature, increased levels of calcium are functionally associated to the main features and risk factors of AD: presenilin and amyloid precursor protein (APP) mutations, ApoE4 expression, beta amyloid plaques (A$\beta$), synaptic dysfunction, tau hyperphosphorylation, and apoptosis. Furthermore, the histopathological features of AD, once formed, can further increase the calcium levels, resulting in fast feed-forward acceleration once the disease process has taken hold. (Stutzmann 2007). The current data on curcumin and A$\beta$ has showed that curcumin can cross the BBB and prevent A$\beta$ aggregation, and protect neurons from different toxic insults due to A$\beta$ and aging in humans. It is also reported that curcumin improves cognitive decline and synaptic functions in AD animal models (Reddy et al., 2018). In another study, authors reported that curcumin improved the mitochondrial fusion activity, synaptic proteins and mitochondrial function in human neuroblastoma (SHSY5Y) cells (Reddy et al., 2016). In another study curcumin was found to reduce oxidative stress and neurodegeneration and improve locomotor activity, in AD rat model (Huang et al., 2016).

### 2.7. PD

PD is another progressive neurological disorder caused due to oxidative stress, mitochondrial dysfunction and neurotoxins or genetic factors such as PTEN induced kinase 1 (PINK1), $\alpha$-synuclein, DJ-1, and leucine rich repeat kinase 2 (LRRK2) and leading to motor symptoms that include hypokinesia, rigidity, and tremor. The most marked neuropathological feature dopaminergic neuronal loss in the substantia nigra pars compacta, resulting in dopamine reduction in the target area, the striatum. Some neurons in the substantia nigra possess intracytoplasmic inclusions known as Lewy bodies. (Lotharius and Brundin 2002). In one study curcumin pre-treatment saved cell viability, enhanced MMP, improved mitochondrial respiration in control cells, reduced apoptosis and enhanced MMP and maximal respiration in *PINK1* siRNA cells. (Van der Merwe et al., 2017).

In PD there is abnormal deposition and aggregation of the presynaptic protein $\alpha$-synuclein in the dopaminergic neurons as Lewy bodies (LBs). Sharma and Nehru in 2018 reported that curcumin administration reduced $\alpha$-synuclein aggregates in the dopaminergic neurons and downregulated NF$\kappa$B, proinflammatory cytokines (IL-1$\beta$, TNF-$\alpha$, and IL-1$\alpha$), and iNOS. Curcumin also improved significantly the glutathione system (GSH and redox ratio) (Sharma and Nehru 2018). Furthermore Wang and the co authors reported that curcumin reduced injury in PD rats due to oxidative stress *via* the Wnt/$\beta$-catenin signaling pathway (Wang et al., 2017a). In another study curcumin improved locomotive abilities and reduced neurodegeneration in PD induced *Drosophila* model (Nguyen et al., 2018). In a current study curcumin reduced neurotoxic effects, degenerative histological changes and oxidative stress in the cerebellar cortex of a PD rat model (Fikry et al., 2022)

## 3. Approaches to overcome the poor solubility of curcumin

The poor solubility of curcumin imposes a challenge for its therapeutic activity. Many approaches have been successful for enhancing the solubility and thus bioavailability of curcumin. Some of the examples are given below. Some of the animal and human studies of different curcumin formulations in treating different diseases are described in Table 5 and Table 6 respectively. Furthermore, some of the completed and ongoing clinical trial of curcumin are summarized in Table 7.

### 3.1. Nanosuspension

Nanosuspensions are colloidal dispersions of submicron sized drug particles which are stabilized by surfactants. These consist of the poorly aqueous soluble drug without any matrix material suspended in dispersion. These can be used to increase the solubility of drugs which are not soluble in lipid as well as aqueous media. Many studies have reported solubility enhancement of curcumin by formulation of nanosuspension. Jiang et al. formulated and characterized nanosuspension of curcumin for the treatment of atherosclerosis used polyvinylpyrrolidone (PVPK30) and sodium dodecyl sulfate (SDS) as stabilizers. The particle size was found to be 78.1 $\pm$ 5.4 nm, the PDI of 0.10 $\pm$ 0.08, and the zeta potential of $-$22.5 $\pm$ 1.2 mV. The curcumin nanosuspension was easily engulfed into RAW264.7 cells in comparison to raw curcumin and deposited more under ultrasound stimulation. The results of in vivo experiments showed that the developed formulation decreased the level of TC and LDL and, relieved atherosclerosis syndrome (Jiang et al., 2020). In another study curcumin nanosuspension was prepared using a cost-effective time saving technique. The solubility and dissolution of curcumin was remarkably enhanced using TPGS or Brij78 as stabilizers. The oral bioavailability of curcumin was increased 3.7 and 3.18 folds after administration of CUR/Brij78 or CUR/TPGS nanosuspensions in comparison to supplementation of curcumin suspension (Wang et al., 2017c). Wang and the co-authors used the antisolvent precipitation technique for fabricating the amorphous nanosuspension of curcumin. The size range of developed nanosuspensions was 150–175 nm with unimodal size distribution resulting in 35-fold increase in solubility. An in-vitro investigation on Caco-2 cell lines revealed a noteworthy enhancement in curcumin bioavailability when it was stabilized using $\beta$-lactoglobulin (Wang et al., 2017c).

### 3.2. Solid dispersion

A solid dispersion is fundamentally a two-component system consisting of a drug and a polymer in which the dispersion mechanism of drug is the key to understanding its behavior. In one of the studies sustained-release solid dispersion of curcumin was formulated using hot melt extrusion to increase its solubility. The prepared formulation

**Table 5**
Preclinical studies of different curcumin formulations.

| S.N | Formulation | Disease | Animal | Dose | Number of animals | Results | Reference |
|---|---|---|---|---|---|---|---|
| 1. | NPs | Doxorubicin induced cardiotoxicity | Wistar Albino rats | 50 mg/kg for 2 weeks | 9 | Decreased cardiotoxicity and tachycardia. Decreased NO, MDA, dopamine, AchE and LDH and doxorubicin induced decrease in GSH, 5-HT and Na,K,ATPase | (Mohammed et al., 2020) |
| 2. | PLA-PEG NPs | Liver inflammation | Albino rats | 20 mg/kg/bw | 10 | Reduced inflammation and oxidative stress decreased serum NF-κB, hepatic COX-2 and TGF-$\beta$1 and increased PPAR-$\gamma$ | (El-Naggar et al., 2019) |
| 3. | NP-hydrogel | Skin wound | Albino rats | 1 mL gel (7.5 mg/mL | 10 | Increased wound healing via increased wound closure rate, collagen deposition, granulation tissue formation, VEGF production and AQP3 expression | (Kamar et al., 2019) |
| 4. | Curcumin capped gold loaded PLGA NPs | Cardiac anti-hypertrophy | Male Wistar rats | 40 mg/kg/day for 10 weeks | | Increased anti-inflammatory and antioxidant actions, controls cardiomyocyte growth and prevents myocardial infarction. Enhanced survival rate and better cardiac functions in cardiac anti-hypertrophy. | (Liu et al., 2019b) |
| 5. | Solid dispersion | – | SD rats | 100 mg/kg | 6 | Enhanced sustain release effect, increased solubility and bioavailability, prolonged the residence time | (Fan et al., 2019a) |
| 6. | Lipid based NPs | Retenosis | SD rats | 100 microlitre | 6 | Enhanced anti-restenosis effect and increased inhibition of neointimal formation | (Akhlaghi et al., 2019) |
| 7. | Nanocapsules | AD | Swiss male mice | 10 mg/kg 12 days | | Reduction in $\beta$-Amyloid generated oxidative stress in the prefrontal cortex, demonstrated by the enhancement in the reactive species levels, catalase and superoxide dismutase activities | (Fidelis et al., 2019) |
| 8. | Poly d,l-lactic-co-glycolic acid NP | Immunomodulation | Albino mice | 5 mg/kg/bw for 10 days | 5 | Increased humoral immune response, white blood cells and antibody production | (Afolayan et al., 2018) |
| 9. | PLA NPs | MI | Guinea pigs | 10 and 21 mg/kg for 7 days | 5 | Reduced atrial fibrillation CTnI and kidney injury molecule-1 | (Nabofa et al., 2018) |
| 10. | Nanoliposomes | DCP | SD rats | 5 mg/kg for 12 weeks | 15 | Improved cardiac function by reducing apoptosis and fibrosis in myocardial cells | (Mao et al., 2018) |
| 11. | PBLG-PEG-PBLG Nps | | SD rats | 20 mg/kg for 8 weeks | 10 | Reduced myocardial injury, increased $H_2S$ and $[Ca^{2+}]$ levels | (Tong et al., 2018) |
| 12. | PLGA NPs | Glioblastoma | Glioma-2 rats | 25 $\mu$M for 5 days | 5 | Increased cytotoxicity of Glioma-2 cells | (Orunoğlu et al., 2017) |
| 13. | Magnetic hydrogel nanocomposite | CVD | Albinorats | 5 mg/kg for 2 weeks | 10 | Increased GPX and SOD, and reduced MDA in cardiac tissue | (Namdari and Eatemadi 2017) |
| 14. | SNEDDS | DN | SD rats | 30 100 and 300 mg/kg for 2 weeks | | Reduced neuroinflammation and enhanced antioxidant defense | (Joshi et al., 2013) |
| 15. | alginate-curcumin nanocomposite | PD | Drosophila | $10^{-5}$, $10^{-3}$, and $10^{-1}$ g/mL for 24 days | | Reduced oxidative stress and brain neurodegeneration | (Siddique et al., 2013) |
| 16. | NLC | CNS activity | Male CD1 | 100 mg/kg for | 5 | Increase in hypoacetylation of histone 4 at lysine 12 in the spinal cord. Increase in the pharmacokinetics of curcumin leading to a better permeation in the CNS | (Puglia et al., 2012) |

PLGA: Poly (lactic-co-glycolic acid); PLA-PEG: Poly lactic acid-poly ethylene glycol; PBLG: Poly (gamma -benzyl-l-glutamate); CNS: Central nervous system; AchE: Acetylcholinesterase; LDH: Lactate dehydrogenase; 5-HT: 5 hydroxy tryptamine; AQP3; Aquaporin 3; CTnI: cardiac troponin I.

showed increased solubility and had a noteworthy sustained-release effect in comparison to raw curcumin (Fan et al., 2019b). In another study the authors have formulated solid dispersion of curcumin with enhanced solubility as well as increased cytotoxicity against all tumor cell lines tested (breast adenocarcinoma and lung, cervical and hepatocellular carcinoma)(Silva de Sá et al., 2019). Furthermore solid dispersion of Zinc(II) complexes of curcumin was prepared by Wu and the co-authors. In vitro assays discovered that the developed formulation decreased the HepG2 and SK-HEP1 cell survival and effectively improved inhibition of cell growth and apoptosis due to doxorubicin. The anticancer actions were also observed in animals after oral supplementation of formulation, without any change in animal weight. Moreover, supplementation of the developed formulation individually or when combined with doxorubicin significantly reduced dysbiosis of the gut in rats (Wu et al., 2019). In another research it was discovered that solid dispersion enhanced the curcumin dissolution (buffer pH 6.8) with almost 90% drug release in 1 h. The formulation also exhibited enhanced bioavailability as calculated from the pharmacokinetic study in rats (Seo et al., 2012). Similarly, in another research curcumin solubility and bioavailability was enhanced by formulating its solid dispersion using spray drying technique. Dissolution outcomes revealed that the release profile of drug was affected by pH values. The release speed was increased at lower pH values (pH 1.2). Curcumin in pH 1.2 had an insignificant release (less than 5%) beyond 120 min whereas, solid dispersion showed a drug release of upto 45% after 60 min (Gangurde et al., 2015).

### 3.3. Nanoparticles (NPs)

NPs are the tiny particles ranging in size from 1 to 100 nanometer have shown promising effects in enhancing the solubility and bioavailability of curcumin in various studies. Mirzahosseinipour et al. formulated silica nanoparticles of curcumin which exhibited photodynamic inactivation actions against planktonic as well as biofilm form of *P. aeruginosa* and *S. aureus*. The NPs showed wound healing activity and had no significant toxicity against human normal fibroblast cells (Mirzahosseinipour et al., 2020). Furthermore Kumari et al. in 2021 formulated Poly-glycerol-malic acid- dodecanedioic acid NPs

**Table 6**
Clinical studies of different curcumin formulations.

| S.N | Formulation | Disease | Design | Subjects | Duration | Dose | Results | Reference |
|---|---|---|---|---|---|---|---|---|
| 1. | Nano curcumin | Diabetic Sensorimotor Polyneuropathy | P DB R PC | 40 | 8 weeks | 80 mg | Decrease in FBG, HbA1c, total score of neuropathies, total reflex score and temperature | (Asadi et al., 2019) |
| 2. | Phospholipid lecithin formulation | ... | Open label | 11 | 3 months | | Improved visual acuity and reduced macular edema | (Mazzolani et al., 2018) |
| 3. | Nano micelle | DM | R DB PC | 35 | 3 months | 30 mg | Decrease in FBG and HbA1c and improvement in lipid profile | (Rahimi et al., 2016) |
| 4. | Phytosomes | | R DB PC | 56 | 8 weeeks | 200 mg | Reduced BGL and TGsImproved HOMA index, waist circumference, HDL-C, and liver transaminases | (Cicero et al., 2020) |
| 5. | Bioavailable curcumin formulation, CurQfen® | Cardiovascular disease risk factors and arterial function | DB PC | 22 | 12 weeks | 500 mg/day | improved homocysteine and HDL concentrations, thus promoting favourable cardiovascular health in obese men. | (Campbell et al., 2019) |
| 6. | Phytosomes | NAFLD | R | 43 | 8 weeks | 1000 mg/ day | Reduced liver fat and improver transaminase levels | (Panahi et al., 2016d) |
| 7. | Nano micelle | OA | R DB | 36 | 6 weeks | 80 mg/day | Reduced pain and muscle stiffness | (Hashemzadeh et al., 2019) |
| 8. | Solid lipid curcumin particles | | R DB | 17 | 90 days | 160 mg | Reduced inflammatory markers with no side effects | (Gupte et al., 2019) |
| 9. | Nano micelle | RA | R DB PB | 30 | 12 weeks | 120 mg | Improved disease activity score−28 and swollen joint count | (Javadi et al., 2019) |
| 10. | Theracurmin | Memory impairment | R DB PC | 21 | 18 months | 180 mg | Improved memory and attention | (Small et al., 2018) |

loaded with curcumin for the treatment of breast cancer. The developed NPs exhibited enhanced anticancer activity towards breast cancer cell lines (MCF-7 and MDA-MB 231) compared to raw curcumin (Kumari et al., 2021).In another research hybrid antibacterial agent was formulated based on silver NPs and curcumin. Oxidized amylose was used as reducing agent for formulating silver NPs. Solubility of curcumin was enhanced by encapsulating into oxidized amylose. The formulated hybrid antibacterial agent revealed increased antibacterial and antioxidant actions (Lyu et al., 2020). Furthermore, NPs loaded with curcumin were formulated with enhanced solubility and a mean particle size of 149.0 ± 2.2 nm. The NPs showed 96% of entrapment and increased biocompatibility with glial and neuronal cells. The cellular uptake of NPs was stimulated by surface characterization (Del Prado-Audelo et al., 2019). In another study kafirin solid and hollow NPs loaded with curcumin were prepared using electrostatic layer-by-layer (LbL) deposition of Chitosan/Dextran sulphate components using sodium carbonate as a sacrificing template for the hollow NPs. The prepared NPs were compared for their encapsulation as well as structural and release properties. Enhanced dissolution profiles in gastrointestinal tract was noted for curcumin after loading into solid as well as LbL NPs in comparison to raw curcumin; while the hollow structure of LbL NPs revealed less release of curcumin in comparison to solid NPs(Li et al., 2019b). In a research conducted by Ban and the co-authors reported that long-PEGylated solid lipid NPs loaded with curcumin quickly permeated the epithelium due to the neutral surface charge of the micelles, leading to a greater than 12.0−fold enhancement in bioavailability in comparison to raw curcumin solution in a rat model (Ban et al., 2020). In a recent study methotrexate and curcumin co-encapsulated PLGA NPs were synthesized which showed significantly increased cytotoxicity as compared to free methotrexate and curcumin or even their solo-loaded formulations. The in vivo results revealed the synergic actions of methotrexate and curcumin co-delivery on impeding the development of breast cancer. Curcumin could increase the loading efficacy of methotrexate in PLGA NPs (Vakilinezhad et al., 2019). Liu et al. fabricated novel composite NPs using bio-based materials wherein the physicochemical properties of NPs were controlled by the shell structure. The NPs possessed higher curcumin loading capacity and very good redispersibility. Nanoencapsulation markedly enhanced the photochemical stability and antioxidant properties of curcumin (Liu et al., 2019a).

Singh et al. reported the fabrication of a biodegradable liposome gold NP loaded with curcumin for treatment of skin cancer. The developed curcumin NPs had a remarkably increased uptake in comparison to raw curcumin. Improvement in cancer cell cytotoxicity was noted in curcumin loaded gold NPs treated group upon laser irradiation owing to curcumin (Singh et al., 2018). Moreover, curcumin formulated in solid lipid NPs resulted in enhanced curcumin plasma levels in mice. In addition, the developed NPs decreased the expression of proteins necessary for cell apoptosis as well as cell proliferation (XIAP and Mcl-1) in Hodgkin's lymphoma tumor extracts. In Hodgkin's lymphoma cells in culture, curcumin reduced the expression of related anti-inflammatory cytokines (IL-6 and TNF-$\alpha$) in a concentration-dependent manner (Guorgui et al., 2018) Moreover in another study core shell biopolymer NPs increased the DPPH radical scavenging activity of curcumin after encapsulation inside the NPs, whereas prolonged the drug release in GIT (Li et al., 2021). In another study, zein/carboxymethyl dextrin NPs were successfully formulated which exhibited enhanced encapsulation efficiency of curcumin (85.5%). Morever the antioxidant activity and photothermal stability of curcumin were remarkably increased after loading it into NPs. The curcumin release was also extended in simulated GIT fluids (Meng et al., 2021).

Electrospun PVP-Core/PHBV-Shell fibers were fabricated to erradiate tailing off to achieve better sustained release of curcumin (Liu et al., 2021) In a current study, for the first time, the synergistic activity of curcumin and silver/copper NPs was explored against Staphylococcus aureus and Pseudomonas aeruginosa. The developed formulation enhanced the inhibition zone by about 6 mm (Targhi et al., 2021). In another study the solubility of curcumin was increased 2627 folds by formulating PLGA nanobubbles. Importantly, when the developed formulation was combined with Low-intensity focused ultrasound it permeate though the blood brain barrier and locally deliver the curcumin into the deep-seated brain nuclei, remarkably increasing curcumin efficacy in the PD C57BL/6 J mice model in comparison with curcumin nanobubbles alone (Yan et al., 2021).

### 3.4. Emulsions

Another approach to enhance to bioavailability of curcumin is formulation of emulsion. Different type of emulsions such as nano

**Table 7**
Clinical trials of curcumin (https://clinicaltrials.gov/ct2/results?cond=&term=Curcumin&cntry=&state=&city=&dist= (Accessed on 23/5/2020)).

| S.N | Condition | Status | Phase | Design | Study start | Study completion |
|---|---|---|---|---|---|---|
| 1. | Cognitive function | Completed (RNP) | 2 | R DB PC | August 11, 2017 | October 18, 2019 |
| 2. | Prostate cancer | Completed (RNP) | NA | R DB PC | August 30, 2007 | August 5, 2015 |
| 3. | | Recruiting | Phase 3 | R SB DB | May 2014 | June 2020 |
| 4. | | Completed (RNP) | NA | R PD DB | March 2011 | October 2013 |
| 5. | | Recruiting | Phase 3 | R DB PC | March 11, 2019 | March 11, 2019 |
| 6. | | Terminated | Phase 2 | R PD TB | March 2014 | April 2018 |
| 7. | Cognitive impairment | Completed (RP) | Phase 2 | R PD Quadruple | March 2012 | April 2017 |
| 8. | | Terminated (RP) | NA | SB OL | May 2005 | June 2008 |
| 9. | Breast cancer | Recruiting | Phase 1 | SG OL | January 29, 2020 | November 30, 2021 |
| 10. | | Recruiting | NA | R PD DB | March 4, 2019 | July 31, 2020 |
| 11. | | Completed (RP) | Phase 2 | R PD Quadruple | January 2008 | April 2011 |
| 12. | | Active Not recruiting | Phase 2 | R PD Quadruple | une 18, 2017 | December 31, 2020 |
| 13. | | Completed (RP) | Phase 2 | R DB PC | May 2015 | July 27, 2018 |
| 14. | | Completed (RP) | Phase 2 | R PD DB | October 13, 2015 | September 30, 2016 |
| 15. | Pancreatic cancer | Completed (RNP) | Phase 2 | NR SB OL | July 2004 | September 2010 |
| 16. | | Completed | Phase 2 | SB OL | November 2004 | April 2014 |
| 17. | Endometrial cancer | Completed | Phase 2 | SB OL | October 2013 | October 2016 |
| 18. | IBS | Recruiting | NA | Quadruple PD | August 1, 2018 | March 2028 |
| 19. | | Completed (RNP) | Phase 1 | SB OL | May 2009 | June 2010 |
| 20. | | Completed 9RNP) | Phase 4 | R PD Quadruple | November 2008 | June 2009 |
| 21. | | Not yet recruiting | NA | R PD Quadruple | July 2018 | December 2020 |
| 22. | Lung cancer | Unknown | Phase 1 | OL | August 2015 | December 2016 |
| 23. | Schizophrenia | Terminated | NA | R PD Quadruple | February 11, 2016 | August 24, 2017 |
| 24. | NAFLD and IR | recruiting | NA | R PD DB | March 5, 2019 | October 2020 |
| 25. | Ulcerative colitis | Recruiting | NA | R DB PC | June 19, 2017 | April 2021 |
| 26. | | Recruiting | Phase 3 | R DB PC | March 1, 2020 | December 31, 2022 |
| 27. | | Completed | Phase 3 | R DB PD | July 2011 | October 2014 |
| 28. | Cognitive impairment | Active Not recruiting | Phase 2 | R quadruple | January 20, 2014 | May 31, 2020 |
| 29. | CVD | Recruiting | NA | R CO DB | January 4, 2019 | July 30, 2020 |
| 30. | Atherosclerosis | Phase 2 | Unknown | R CO SB | September 2016 | December 2018 |
| 31. | Colon cancer | Recruiting | Phase 1 | R OL | January 2011 | December 2022 |
| 32. | | Completed (RNP) | Phase 2 | R PD OL | February 2012 | May 31, 2017 |
| 33. | T2DM | Unknown | Phase 4 | R SB PD | August 2009 | April 2010 |
| 34. | | Unknown | Phase 3 | R PD DB | August 1, 2018 | April 30, 2019 |
| 35. | | Unknown | Phase 4 | R PD SB | July 2009 | March 2010 |
| 36. | | Unknown | Phase 3 | R PD Quadruple | February 2017 | October 2017 |
| 37. | . . . | Completed (RNP) | NA | NA | September 16, 2019 | December 2, 2019 |
| 38. | | Unknown | Phas 1 | R PD Quadruple | April 2016 | January 2017 |
| 39. | DNP | Unknown | Phase 3 | R PD TB | August 1, 2018 | April 30, 2019 |
| 40. | Crohn's disease | Completed (RNP) | Phase 3 | R PD DB | December 2014 | June 2018 |
| 41. | | | | | | |
| 42. | Schizophrenia | Completed (RNP) | Phase 4 | R SB | January 2015 | May 2017 |
| 43. | Prediabetes | Recruiting | Phase 4 | R PD TB | February 25, 2019 | February 28, 2020 |
| 44. | Colorectal cancer | Completed | Phase 2 | SB OL | August 24, 2015 | August 1, 2019 |
| 45. | | Active Not recruiting | Phase 1 | R SB OL | June 2013 | October 5, 2019 |
| 46. | Metabolic syndrome | Active Not recruiting | NA | SB OL | September 19, 2018 | November 2020 |
| 47. | | Completed (RNP) | NA | R PD DB | May 6, 2018 | December 6, 2019 |
| 48. | | Completed (RNP) | Phase 2 | R CO | July 2013 | October 2014 |
| 49. | Cervical cancer | Not yet recruiting | Phase 2 | R PD DB | June 1, 2020 | December 31, 2023 |
| 50. | OA | Not yet recruiting | NA | R PD DB | December 18, 2019 | June 30, 202 |
| 51. | | Completed | Early phase 1 | SB OL | March 2012 | December 2012 |
| 52. | Inflammation | Completed | NA | R CO TB | October 2013 | March 2015 |
| 53. | | Completed | NA | R PD DB | November 30, 2016 | August 28, 2017 |
| 54. | AD | Unknown | Phase 2 | R SB DB | October 2009 | November 2010 |
| 55. | | Completed | 2 | R PD DB | October 2004 | July 2006 |
| 56. | | Completed | 2 | R PD DB | July 2003 | December 2007 |
| 57. | RA | Unknown | Early phase 1 | R CO DB | January 2010 | January 2011 |

RNP: Results not posted; RP: Results posted; R: Randomized; DB: Double blind; PC: Placebo control: SB: Single blind TB: Triple blind; CO: Cross-over; OL: Open label; NR: Non random.

emulsion, self nano-emulsifying drug delivery system (SNEDDS) and self micro-emulsifying drug delivery system (SMEDDS) have been formulated. Joshi et al. formulated SNEDDS of curcumin which increased the bioavailability of curcumin thus leading to enhanced protection of diabetic neuropathy in comparison to unprocessed curcumin. The developed formulation had a provided better result against behavioural functional and biochemical deficits (Joshi et al., 2013). Furthermore, in one of the study the SMEDDS tablet increased the solubility of curcumin and an *in-vitro* study revealed a pulsatile release with a precise lag time. The ratio of H-pectin/lactose play a significant role in regulating the lag time which maintains the effectiveness of colon-specific delivery. When rat cecal and pectinase content were added in the dissolution media, the erosion time got prominently reduced, demonstrating that the H-pectin plug is delicate to degradation by enzymes (Huang et al., 2013b). Another study focussed on formulating polysaccharide based nanoemulsion containing curcumin. Olive oil and castor oil, and different polysaccharides such as alginate and $\kappa$-carrageenan were assessed for the entrapment efficacy. The formulation containing $\kappa$-carrageenan fucoidan possessed comparatively better properties in comparison nanoemulsions fabricated with other surfactants such as tween 20. Use of fucoidan as a surfactant resulted in an emulsion with the

smallest size. Thermodynamic and rheological results revealed improved stability profile of developed nanoemulsion. Synergistic enhancement for the antioxidant actions of the formulated curcumin nanoemulsion was also remarkable (Richa and Roy Choudhury 2019). In another study SNEDDS were formulated comprising of an optimal formula of ethyl oleate:tween 80:PEG 600 (50:40:10% w/w) with 11.2-nm uniform droplets was developed for curcumin delivery. The drug loading for curcumin was evaluated orally in rat. The results revealed a prominent enhancement of 3.95 folds in $C_{max}$, and the bioavailability of curcumin was increased by 194.2%, in comparison to the curcumin suspension in water (Nazari-Vanani et al., 2017). In a recent study Khursheed et al. formulated SNEDDS loaded with curcumin and quercetin. The developed SNEDDS formulation showed a drug release of more than 90% in first five minutes whereas in case of raw curcumin and quercetin less than 20% drug release was obtained in 60 min (Khursheed et al., 2021). In another study the developed SNEDDS of curcumin and quercetin could significantly reduce BGL and improve lipid biomarkers in HFD/STZ induced diabetic rats (Khursheed et al., 2022)

### 3.5. Nanostructured lipid carriers (NLCs)

NLCs are the drug delivery system where an aqueous phase consisting of emulsifier(s) contains dispersed partial-crystallized lipid particles (mean radii $\leq$ 100 nm). NLC are a beneficial delivery system for nutraceuticals with high encapsulation efficiency, drug loading, and stability.

In one of the study curcumin permeability was enhanced 30 times across Caco-2 cell monolayers in nanocapsules as compared to SNEDDS and its suspension. The curcumin SNEDDS and curcumin NLC prominently decreased secretion of TNF-$\alpha$ by macrophages. When used in-vivo, there was a reduction in neutrophil infiltration and inflammation of the colon by curcumin NLC and curcumin SNEDDS did not show any effects (Beloqui et al., 2016). In another *in-vivo* study Wolf et al. compared curcumin NLC and nanoemulsion for various physiological skin parameters for a duration of 4-weeks and reported higher penetration effect of curcumin from NLC in comparison to emulsion (Wolf et al., 2018). In a recent study cellulose nanofibre film was fabricated as a topical formulation by hybridizing NLCs loaded with curcumin. The in vivo test for anti-psoriatic potential showed that the developed films reduced the symptoms of psoriasis in mice, and exhibited anti-inflammatory activity almost equivalent to a marketed corticosteroid cream for topical use. The outcomes could be ascribed to the increased deposition of curcumin and the membrane hydration activity provided by the film (Kang et al., 2018). Furthermore, protein free NLC similar to lipoprotein containing curcumin was formulated which showed improved stability. The developed NLC revealed markedly increased affinity for bEnd.3 cells but with reduced uptake in macrophages. Studies on *ex vivo* imaging further established that the developed NLC could successfully cross the blood brain barrier and differently accumulate in the brain (2.38 times greater than NLC) (Meng et al., 2016). Riaz and the co authors developed curcumin loaded NLCs for treating of *cutaneous leishmaniasis*. An increased deposition of drug in the outer and deeper skin layers was attained with NLC gel containing curcumin in comparison to reference gel containing curcumin. The in vitro antileishmanial assay against axenic amastigote like cells (AALCs) and promastigotes established curcumin NLCs to be more effective in comparison to raw curcumin solution (Riaz et al., 2019).

### 3.6. Pluronic nanomicelles

Currently, pluronic nanomicelles of curcumin were prepared which was compared with “raw curcumin”, in a STZ induced diabetic rat model; the prepared formulation reduced degradation and hence increased the amount of curcumin delivered in vitro trials. The developed formulation reduced fasting blood glucose (FBG) in rats in comparison to “native curcumin” and it also exhibited a superior effect in the oral glucose tolerance test. The concentration of TGs and cholesterol was reduced to the same extent by both the tested formulations and did not show any noteworthy influence on concentration of insulin in pancreatic tissue. Remarkably, the nanoformulation of curcumin re-established and enhanced the gene expression of two necessary factors for viability and proliferation of pancreatic $\beta$ cells i.e. duodenal homeobox-1 (Pdx-1) and NK6 homeobox-1 (Nkx6.1) (El-Far et al., 2017).

## 4. Conclusion

The potential of curcumin in the treatment of various disorders are well evident from the preclinical and clinical studies discussed in this review. Curcumin act through multiple molecular mechanisms at different molecular targets and provide beneficial and protective role in the treatment and prevention of chronic diseases too. Novel delivery approaches such as nanoparticles, solid dispersions, nanocapsules, SNEDDS, liposomes, NLCs play an important role in overcoming the solubility related issues of curcumin. Nevertheless these drug delivery systems have their own limitations in terms of stability, safety, efficacy and expense. Even though numerous preclinical, cell-line and clinical level studies have been performed to establish the potential candidature of curcumin but still there is a need to formulate more précised and cost effective formulation in the market for societal benefits.

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## Web links

https://clinicaltrials.gov/ct2/results?cond=&term=Curcumin&cntry=&state=&city=&dist= Accessed on 23/5/2020)

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