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Curcumin targeting oxidative mediators for therapeutic effects in diabetes and its related complications

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ABSTRACT: DIABETES mellitus is a multifactorial chronic metabolic disorder characterized by altered metabolism of macro – nutrients such fats, proteins and carbohydrates associated with disturbances in insulin activity. Diabetes mellitus complications include, diabetic retinopathy, diabetic cardiomyopathy, diabetic encephalopathy, diabetic periodontitis and diabetic nephropathy. These complications are mostly induced by inflammatory and oxidative mediators. Curcumin is a polyphenol extracted from turmeric and it is well known for its antioxidant, anti-inflammatory and antiapoptotic activities. It effectively targets oxidative mediators in diabetes mellitus through regulation of several signaling pathways. Insulin resistance is commonly caused due to impairment in the signaling pathways related to insulin and the target tissues pose lesser or no response to circulating insulin. Curcumin is a potent therapeutic agent that targets oxidative stress mediators in diabetes mellitus and its resistant version leading to favorable therapeutic outcomes in diabetes complications. This review has thrown sufficient light on the therapeutic potential of curcumin targeting oxidative mediators in diabetes and its related complications.
Keywords: Diabetes mellitus; Curcumin; Oxidative mediators; diabetes resistance.

1. Introduction

DIABETES mellitus is a chronic metabolic multifactorial disorder accompanied by altered macro – nutrients metabolism due to lack of insulin activity or inability to use it properly (Roglic and Norris, 2018). The World Health Organization (WHO) indicated that about 693 million people will be diabetic at the end of 2030 (Cho et al., 2018). Both types of diabetes mellitus (type 1 and 2) associated complications are life threatening and affect life style (Mohan et al., 2019). These include diabetic retinopathy (Duh et al., 2017), diabetic cardiomyopathy (Borghetti et al., 2018), diabetic encephalopathy (Chen et al., 2020), diabetic periodontitis (Genco and Borgnakke, 2020) and diabetic nephropathy

(Flyvbjerg, 2017). Inflammation ensues when pathogens invades a living system or tissue injury occurs that subsequently infiltrates and activate the adoptive or/and innate immunity system cells and a physiological response is produced, which results in the production of inflammatory cytokines (Maurizi et al., 2018). Release of inflammatory mediators is mediated by oxidative stress and caused by elevated glucose level (Panahi et al., 2018). Thus, the pathophysiology of diabetes mellitus is linked with chronic inflammation and state of oxidative stress. The role of inflammatory mediators in type-2 diabetes mellitus has been confirmed (Araújo et al., 2020). Inflammatory mediators in turn generate reactive oxygen species and oxidative stress (Oguntibeju, 2019). Oxidative stress biomarkers have been detected in diabetes patients (Bigagli and Lodovici, 2019; Rehman and Akash, 2017). Hyperglycemia associated insulin resistance is mainly induced by oxidative stress and inflammation (Chen et al., 2021; Luc et al., 2019). Curcumin is a natural lipophillic polyphenol extracted from turmeric exhibit many therapeutic activities such as, anticancer (Rompicharla et al., 2017), antiulcer (Kwiecien et al., 2019), antimicrobial (de Oliveira et al., 2018), antidiabetic (Den Hartogh et al., 2020) and antioxidant activity (Vollono et al., 2019). Curcumin targets oxidative stress resulting in the management of diabetes mellitus and its related complications. Curcumin affects oxidative stress related to diabetes mellitus mainly by targeting superoxide dismutases following activation of PI3K – Akt, Keap 1 – Nrf2 – ARE signaling (Jayasuriya et al., 2021), down regulation of MAPK signaling and reduction in the reactive oxygen species (Wu et al., 2020). In addition, curcumin targets oxidative stress in insulin diabetes resistance. Curcumin restores dysfunction associated with Nrf2 that leads to diabetes resistance management (Abdelsamia et al., 2019). Curcumin has shown therapeutic potential in the management of resistant diabetes mellitus targeting oxidative stress. Insulin resistance has a prominent role in diabetes resistance that was managed by curcumin through reduction in the expression of SOCS3, STAT3 signaling, increasing level of IRS – 1, Rac – 1 and suppression of phosphorylation of ERK/JNK signaling pathway (Guo et al., 2021a; Jiménez-Osorio et al., 2016). The U.S. Food and Drug Administration (FDA) has classified curcumin to be a safe compound with no toxicity (Yang et al., 2020). Its safety profile along with tolerability and lack of toxicity have been shown in numerous clinical studies, even at 12 g/day high oral doses (Lao et al., 2006). This review article highlights the therapeutic potential of curcumin in diabetes mellitus focusing on oxidative stress associated with diabetes mellitus.

2. Oxidative stress in diabetes

Oxidative stress is significantly associated with diabetes mellitus (**Figure 1)** and it is considered as a potent culprit for diabetes. Oxidative stress leads to insulin resistance and dysfunction of pancreatic β – cells (Newsholme et al., 2019). Thus, oxidative stress leads to diabetic complications that eventually result in death. Impaired insulin secretion leads to diabetes mellitus where hyperglycemia triggers over activation of β – cells. Free fatty acid also trigger the over stimulation of β – cells (Acosta-Montaño and García-González, 2018). In pancreatic β – cells, free fatty acid and hyperglycemia through subnormal antioxidant expression, produces reactive oxygen and nitrogen species that are accumulated and impair the function of β – cells (Tekin and Tekin, 2020). Moreover, high level of free fatty acid upon chronic exposure to β – cells leads to drop the membrane potential of mitochondria that in turn accumulate uncoupled protein – 2 and finally inhibit the production of insulin through opening of ATP sensitive K^+ channels (Ježek et al., 2018). Similarly reactive oxygen species improve MaFA (leucine zipper family member that causes insulin genes transcription) degradation that is directly associated with insulin secretion and β – cells activity (El Khattabi and Sharma, 2013). IL – 1R signaling pathway activates NF – κB signaling that is associated with oxidative stress and leads to apoptosis and damage of β – cells resulting in diabetes (Melloul, 2008). To sum up, free radical formation has worse consequences and leads to diabetes mellitus through β – cells damage and also contributing via apoptosis of pancreatic β – cells. It is obvious that blood hyper glucose level triggers the interaction of insulin with its concerned receptors in liver, skeletal muscles, adipose tissues and other tissues, encourage glucose metabolism and uptake through activation of insulin signaling (Kim et al., 2018). This common phenomenon leads to insulin resistance and eventually diabetes mellitus. Normal insulin signaling is impaired by hyperglycemic and elevated free fatty acid mediated excessive production of reactive oxygen species, resulting in insulin resistance which is a key factor in causing diabetes mellitus (Forrester et al., 2018). This mentioned reactive oxygen over production also mediates inflammation in adipose tissues via activation of proinflammatory proteins contributing to diabetes through inflammation. Apart from it, oxidative stress also targets certain other signaling pathways like JNK, MAPK, p38 etc, which contributes to insulin receptor substrate

(IRS) degradation through enhanced serine phosphorylation thus interrupting insulin signaling, mediates insulin resistance eventually ends up with diabetes mellitus (Volpe et al., 2018). Here, insulin resistance is specifically attributed to inhibition of JNK1, MAPK and IKKβ activation. Tyrosine phosphorylation of Akt/GSK-3 is inhibited by angiotensin II mediated reactive oxygen species that resulted in L6 myotubes insulin resistance (Diamond-Stanic and Henriksen, 2010). Findings of a recent study suggest that GLUT4 is translocated to lysosome through reactive oxygen species elevated level. Interestingly, sarcolemmal membrane is bypassed and translocation is carried out through casein kinase-2 activation that boosts up the retromer complex activity via suppression of trans-Golgi (Hurrle and Hsu, 2017).

In summary, all these findings reveal that insulin resistance and oxidative stress has an important consistent connection with each other that leads to diabetes mellitus.

Pancreatic beta cells neogenesis in a research study was significantly interrupted by free radicals indicating the role of free radicals on proliferation of pancreatic beta cells (Wang and Wang, 2017). Findings of a recent research study suggested that oxidative stress damaged beta pancreatic cells. In vitro activities clearly indicated the disturbance in beta cells through oxidative stress. In addition, hydrogen peroxide in a concentration of 200 μM reduced insulin secretion stimulated by glucose (Miceli et al., 2018).

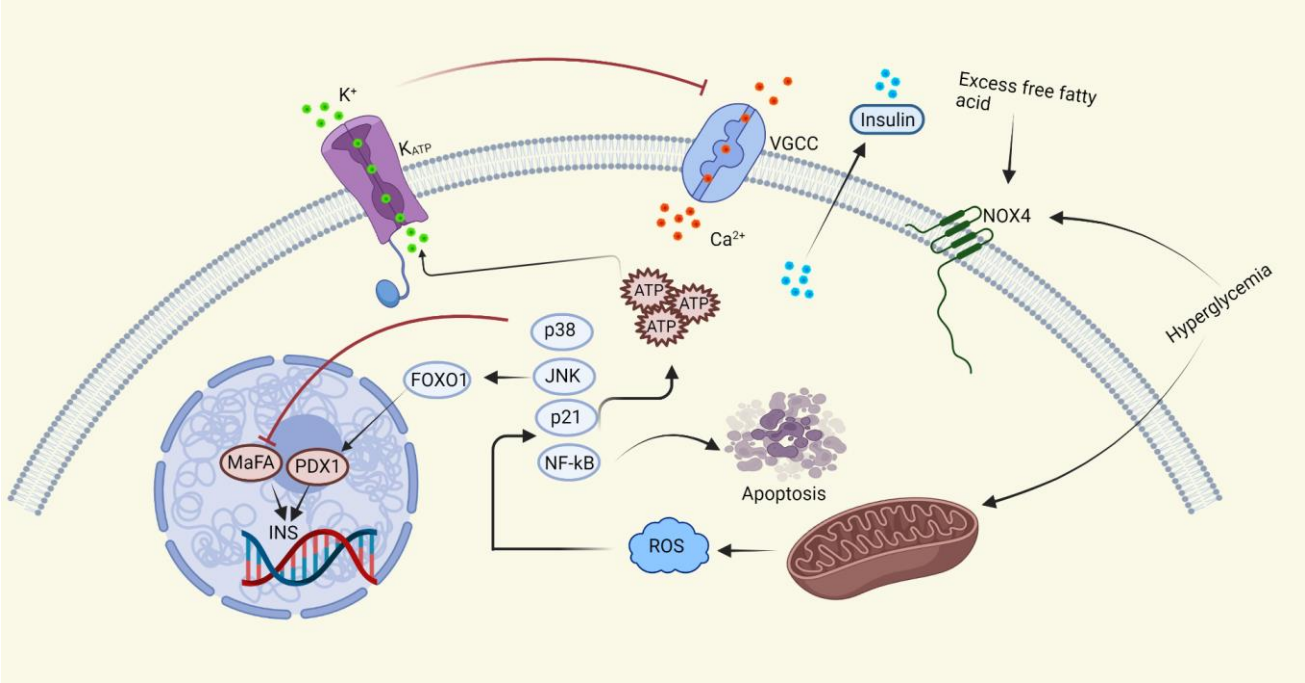

Figure 1: Relationship between oxidative stress and β – cells dysfunction. Pancreatic β – cells apoptosis and reduced insulin secretion are two perspectives mediated by oxidative stress. The over production of reactive oxygen species opens ATP sensitive K^+ channels inhibition of genes transcription related to insulin that in turn suppress insulin secretion and production. In contrast, apoptosis is induced in pancreatic beta cells by oxidative stress activating various signaling pathways like NF – κB, p21, p38 MAPK and JNK. Abbreviations: INS, insulin genes; NF-kB, nuclear transcription factor κB; p21, a cyclin-dependent kinase inhibitor; MaFA, musculoaponeurotic fibro sarcoma protein A; VGCC, voltage-gated calcium channels; KATP, ATP-sensitive K+ channels; NOX4, nicotinamide adenine nucleotide phosphate oxidase; PDX1, pancreas duodenal homeobox factor 1; p38 MAPK, p38 AMP-activated protein kinase; JNK, c-jun N-terminal kinase; FOXO1, forkhead box protein O 1.

In a nutshell, in diabetic patient new therapeutic intervention could be targeted where beta cells dysfunction mediated by oxidative stress could be considered as tuning site. It is suggested that use of such an agent that control oxidative stress and inflammation at pancreatic site hopefully cope with glucose homeostasis eventually improve the life quality of diabetic patients.

To restrict the process of viral replication, innate immune cells produce responses that are attributed to the release of proinflammatory cytokines. However, a negative effect may be inherited such proinflammatory cytokines, due to their role in the etiology of infectious inflammatory diseases (Carty et al., 2021). It has been shown that chemokine and cytokine encoded genes expression was regulated by NF – kB and led yo the regulation of the inflammasome (Prasad et al., 2014). In this context, curcumin as nutraceutical has shown potent anti-inflammatory properties by modulating the expression of IL – 1β, TNF – α, and NF – kB (Boyanapalli et al., 2018). In addition, curcumin by targeting NF – kB signaling significantly has been shown to block viral replication (Ferreira et al., 2015).

3.Therapeutic potential of curcumin: an overview

Curcumin is extracted from *Curcuma longa* (turmeric) and is a lipophillic polyphenol by nature. The yellow color of the turmeric owes to curcumin and is present in abundance along with other curcuminoids – 10 to 20% of curcumin used commercially. Nutraceuticals are the semi synthetic derivatives of curcumin (Fernández-Moriano et al., 2019). Chemical structure of curcumin is shown in **Figure 2.**

Curcumin is effective against edema and inflammation. In a research study, vasodilatation was induced in mice ear using dimethylbenzene. The resultant effect was treated with curcumin in a concentration of 0.05 – 1 g/kg dose for 7 days (Gupta et al., 2013). Curcumin was evaluated for its antiinflammatory potential in a rat model for the treatment of osteoarthritis. Results suggested that curcumin significantly reduced the expression of cytokine level in synovial fluid targeting TLR4/NF-κB signaling pathway (Zhang and Zeng, 2019). The effect of curcumin on inflammatory indices was evaluated in a randomized control study. Results of the study indicated an outstanding reduction in inflammation through reduction in TNF – α, concluding that curcumin play a key role in inflammation suppression in hepatic patients with nonalcoholic fatty liver disorders (Saadati et al., 2019). Systemic infection such as sepsis is a crucial factor in organ failure and sepsis acute kidney injury (SAKI) is one among them. The therapeutic effect of curcumin was explored in SAKI using mice and SAKI cell models. Findings of the study revealed that curcumin reduced the expression of IL – 6, TNF – α, NF – κB signaling pathway and reduced the rate of cell apoptosis resulted in healing of kidney injured cells (Zhu et al., 2020). Apart from individual therapy curcumin in combination therapy has shown significant antiinflammatory action. In this regard, hyperlipidemia induced inflammation was targeted by combined delivery of curcumin and rutin in wistar rats, showing increased HDL and decreased triglyceride levels (Manzoni et al., 2019). It is therefore suggested that curcumin may have the potential to treat inflammation.

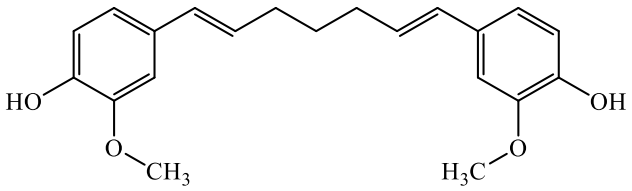

Figure 2. Chemical structure of curcumin

Asthma and allergies are mainly mediated through inflammatory cytokines. Curcumin has been reported for its regulation potential against these inflammatory cytokines in allergy and asthma. The respective mechanism involved is interleukin inhibition and regulation of histamine release from mast cells (Pulido-Moran et al., 2016). It has been recently reported that progranulin is actively associated with psoriasis aetiology. A psoriatic skin lesion mice model under progranulin deficient condition was used in a recent research study. In the absence of progranulin, increase level of proinflammatory cytokines, epidermal thickening and a change in cell differentiation was observed. Curcumin interestingly alleviated progranulin deficiency

induced exacerbation of psoriasis (Zhou et al., 2021). It means that curcumin has a protecting role in lesion exacerbation during psoriasis. Similarly, curcumin was evaluated for its topical delivery in psoriasis. Nano emulgel of curcumin was fabricated via low energy emulsification method and was integrated into hydrogel. Results of the study showed an improved efficacy of curcumin in psoriasis from nano platform (Algahtani et al., 2020a). Another research study on cutaneous infections was carried out that suggested the important role of curcumin as therapeutic agent. Curcumin effectively worked as adjuvant therapeutic during combinatorial delivery with imiquimod, improved its delivery and reduced the worse side effects associated with alone imiquimod delivery (Algahtani et al., 2020b). In combinatorial delivery system, curcumin – caffeine combination in the form of nano sponges based topical gel was explored for anti-psoriatic activity using imiquimod – induced psoriasis mouse model. Results indicated a significant reduction in induction time for anti-psoriatic activity from 20 to 10 days (Iriventi et al., 2020).

The experimental findings of this study concluding that combination therapy with curcumin significantly augmented the anti-psoriatic activity presenting therapeutic potential of curcumin.

During pathogenesis of cancer, multiple signaling pathways are involved and curcumin represent a potential candidate for the regulation of these signaling pathways. Among these, proinflammatory transcription factor (NF – κB) is involved in the breast cancer cell proliferation. Curcumin down regulates NF – κB signaling pathway thus affecting cell proliferation and invasion contributing in breast cancer treatment (Song et al., 2019). In another breast cancer model, curcumin induced autophagy through down regulation of Akt protein posing a significant management strategy for breast cancer (Guan et al., 2016). These findings suggest the therapeutic potential of curcumin following multiple signaling pathways. The therapeutic effect of curcumin has also been exploited in lung cancer and mechanistic approach for its anticancer potential was targeting JAK2/STAT3 and NF-κB signaling pathways in A549 lung cancer cell line (Ashrafizadeh et al., 2020; Wu et al., 2015).

Table 1: Therapeutic potential of curcumin in various cancers

Cancer type	Pathway	Effects	References
Myelogenous leukemia	modulation of the PTEN/AKT via mediation of miR-21	Tumor suppression	(Taverna et al., 2015)
Gastric cancer	Bax up regulation, Bcl-2 down regulation, PAK1 inhibition, cell cycle arrest at G2/M phase	Cell apoptosis, proliferation suppression and invasion	(Cao et al., 2015; Zhou et al., 2016)
Colorectal cancer	Bcl – 2, ROS, JNK,	Apoptosis, survival reduction	(Ismail et al., 2019)
Hepatic cancer	MAPK, ERK1/2, ERK5	Regulation of epithelial to mesenchymal transition	(Liang et al., 2017)
Brain tumor	PI3K/Akt, NF-κB, Bcl-xL	Mitochondrial dysfunction	(Sak, 2020)

In addition, curcumin via PI3K/Akt signaling suppression and microRNA-192-5p up regulation induces apoptosis in non-small cell lung cancer cells with inhibition of cell proliferation (Jin et al., 2015).

Studies showed that elastases such as neutrophils and α1-antitrypsin elastases are actively involved in proliferation of lung tumor approaching inflammation mechanism (Voynow and Shinbashi, 2021). In vitro and in vivo studies showed that curcumin via up regulation of α1-antitrypsin elastases and repression of neutrophils elastases coped with lung cancer (Xu et al., 2012). A recent study reveals that curcumin

liposomal dry powder and gemcitabine were directly sprayed into the rat with lung cancer. The liposomal dry powder of curcumin showed an enhanced anticancer activity as compared to conventional gemcitabine. The therapeutic potential against diabetes and its related complications (Zheng et al., 2018). Curcumin focuses diabetes following certain primary mechanisms. experimental targets founded were TNF – α, Bcl – 2 and Caspase – 3 (Zhang et al., 2018). Curcumin targeting other cancers are shown in **Table 1.**

4. Curcumin modulation of oxidative mediators

Curcumin have displayed a versatile role in many ailments and as discussed above exhibit antiinflammatory, antiapoptotic and antioxidant potential as their prominent one. Preclinical and clinical studies have shown that curcumin have displayed a versatile role in many ailments and as discussed above exhibit antiinflammatory, antiapoptotic and antioxidant potential as their prominent one. Preclinical and clinical studies have shown its therapeutic potential against diabetes and its related complications (Zheng et al., 2018).

Oxidative stress and other mediators are believed to be actively involved in the mediation of diabetes and its related complications, where curcumin is considered a versatile phytochemical that targets oxidative mediators in the concerned issue. In this context, retinopathy related to diabetes is a major health problem and leading cause of blindness globally that is caused by oxidative stress (Hammes, 2018). Curcumin through down regulation of hypoxia-inducible factor 1 shows antioxidant activity in diabetic mediated retinopathy. In a randomized placebo controlled double blind clinical trial 53 diabetic patients with type 2 DM were evaluated using curcumin at a concentration of 1500 mg t.i.d for ten weeks. Results from total antioxidant capacity indicated that curcumin targets oxidative stress and lead to management of type 2 DM. Curcumin showed positive effect on control of fasting blood glucose level (Hodaei et al., 2019). The additive effect of curcumin with reduced insulin dose was investigated in streptozotocin induced diabetic mice model focusing oxidative damage and antioxidant defense. Insulin was administered to mice and a reduced level of glycemia was observed as compared to normal mice. Combination therapy significantly reduced the biomarkers of oxidative stress with reduction in glycemia, ensuring curcumin as a suitable candidate for the treatment of diabetes mellitus targeting oxidative stress (Gutierres et al., 2019).

Diabetes induced oxidative stress leads to splenic complications. An experimental diabetic rat model was design and diabetes were induced using streptozotocin. Depletion in white pulp associated with spleen damage was observed from histological assessment. These alterations were significantly restored by curcumin. In addition, hyperglycemia induced oxidative stress mediated inflammation behind the screen showed up regulation of inflammatory chemokines and cytokines (Rashid et al., 2017). Similarly, the activity of curcumin was evaluated in type 1 diabetes mellitus rat model focusing oxidative stress. Curcumin was administered to streptozotocin induced diabetic male Sprague – Dawley rats. The elevated oxidative stress was reduced by curcumin via reduction in level of plasma superoxide dismutase (responsible for oxidative stress). Such attenuation was attributed to the activation of Keap1-Nrf2-ARE signaling pathway by curcumin (Xie et al., 2018). To counteract the glycative and oxidative stress in diabetes curcumin was mixed in yoghurt and administered to high-fat diet fed mice. Yoghurt alone reduced the proinflammatory cytokines but showed zero effect on oxidative stress status. Curcumin loaded yoghurt was fed into high fat diet mice that the activity of antioxidant enzymes and reduced lipid per oxidation in liver and kidney (Costa et al., 2020).

Diabetes mellitus and particularly its type – 2 is associated with cardiomyopathy being a serious diabetic complication accompanied with alterations in myocardial function and structure (Tan et al., 2020). To evaluate the role of curcumin against oxidative stress *in vivo* activity was carried out on experimental rat by inducing diabetes through feeding with streptozotocin and high glucose diet. While *invitro* studies were carried out by culturing of H9c2 cardiomyocytes with free fatty acid palmitate and high glucose diet. In streptozotocin – induced diabetic rat high level of oxidative stress related biomarkers were observed. Curcumin treatment significantly attenuated elevated level of superoxide dismutase – responsible for diabetes related cardiomyopathy following PI3K – Akt signaling pathway (Ren et al., 2020). Diabetic encephalopathy is another serious complication accompanied with neuropsychiatric disability,

cognitive dysfunctions and it is believed that oxidative stress is involved in the pathophysiology of diabetic encephalopathy (Guo et al., 2021b). An experimental male Sprague – Dawley rat model was used to explore the role of curcumin in targeting oxidative stress in the brain of diabetic rat. Curcumin enhanced the superoxide dismutase activity and decreased the level of malondialdehyde in diabetic rat brain (Miao et al., 2021). Diabetic nephropathy is a serious complication of type 1 diabetes mellitus accompanied with enhanced oxidative stress (Sagoo and Gnudi, 2020). The kidney healing effect of curcumin induced by oxidative stress was investigated in type – 1 diabetes mellitus rats. Curcumin was administered to male rats in a dose of 130 mg/kg of body weight and animals were evaluated for oxidative stress markers. The diabetes induced elevated level of creatinine, urea and uric acid in serum was significantly attenuated by curcumin in diabetic group of animals and in kidney tissues improved the oxidative toxic stress (Ghasemi et al., 2019). During combination therapy in diabetic nephropathy, curcumin and metformin were co – delivered to type – 1 diabetic rats targeting oxidative stress. Streptozotocin induced type – 1 diabetic rat were administered with curcumin in a dose of 50 or 150 mg/kg and metformin in a dose of 300 or 500 mg/kg of body weight and were observed for total oxidant status, total antioxidant capacity, superoxide dismutase activity, protein, urea and creatinine. Both curcumin and metformin showed significant effects on protein, urea and creatinine however curcumin unlike metformin alone restore the total antioxidant status and capacity with recovered activity of superoxide dismutase (Asadi et al., 2019). The combination therapy of curcumin in targeting oxidative stress in diabetes mellitus seems to be ambiguous as discussed in (Ghasemi et al., 2019), where the combination therapy of curcumin and trigonelline was found ineffective.

Nano curcumin from literature have been shown effective than conventional delivery in the treatment of diabetes. It is attributed to the enhanced bioavailability of curcumin from nano – platform. In a recent research work, diabetes induced oxidative stress was in pancreatic and hepatic tissues was managed by curcumin nano particles. The mechanistic approach involved was down regulation of MAPK and activation of Akt signaling pathways. Study concluded the use of curcumin nano particles for the effective treatment of type – 2 diabetes mellitus (Abdulmalek et al., 2021). Similarly, the mean level of oxidative stress mediators, total antioxidant capacity and activity were restored to original status after treatment with curcumin nano particles in diabetic albino rats (Abu-Taweel et al., 2020). Nano curcumin was administered in a dose of 300 mg/kg of body weight to streptozotocin induced diabetic rats and were investigated for effect of curcumin nano particles on oxidative stress. Results indicated a slight accumulation of superoxide dismutase gene in sample of heart tissue collected from diabetic rats (Abdel-Mageid et al., 2018).

In summary, oxidative stress is a major mediator of diabetes that results in serious consequences and complications. Curcumin and its respective nano formulations targets oxidative stress following through multiple mechanisms and have shown effective outcomes in the treatment of diabetes and its related complications. However, the co – delivery of curcumin for diabetes therapy have shown some ambiguous results during targeting oxidative stress that needs further investigations. Curcumin is involved in improvement of pancreatic beta cell function through targeting oxidative stress and such influence at cellular level is depicted in **figure 4.** Both oxidative stress and inflammatory mediators are interlinked in diabetes mellitus that are influenced by curcumin.

5. Conclusions and future directions

Oxidative stress mediators are involved in the induction of diabetes mellitus. Such consequences include diabetic retinopathy, diabetic cardiomyopathy, diabetic nephropathy, diabetic encephalopathy, diabetic periodontitis and endothelial dysfunction as well. Curcumin has shown efficacy in many conditions given its antiinflammatory, anti-apoptotic and antioxidant potential as their prominent one. Curcumin ameliorates oxidative stress related to diabetes mellitus by targeting superoxide dismutases following activation of PI3K – Akt, Keap 1 – Nrf2 – ARE signaling, down regulation of MAPK signaling and reduction in the reactive oxygen species level that eventually leads to management of oxidative stress associated with diabetes mellitus. In addition, curcumin also targets oxidative stress mediators in insulin diabetes resistance. Curcumin restores dysfunction associated with Nrf2 that leads to

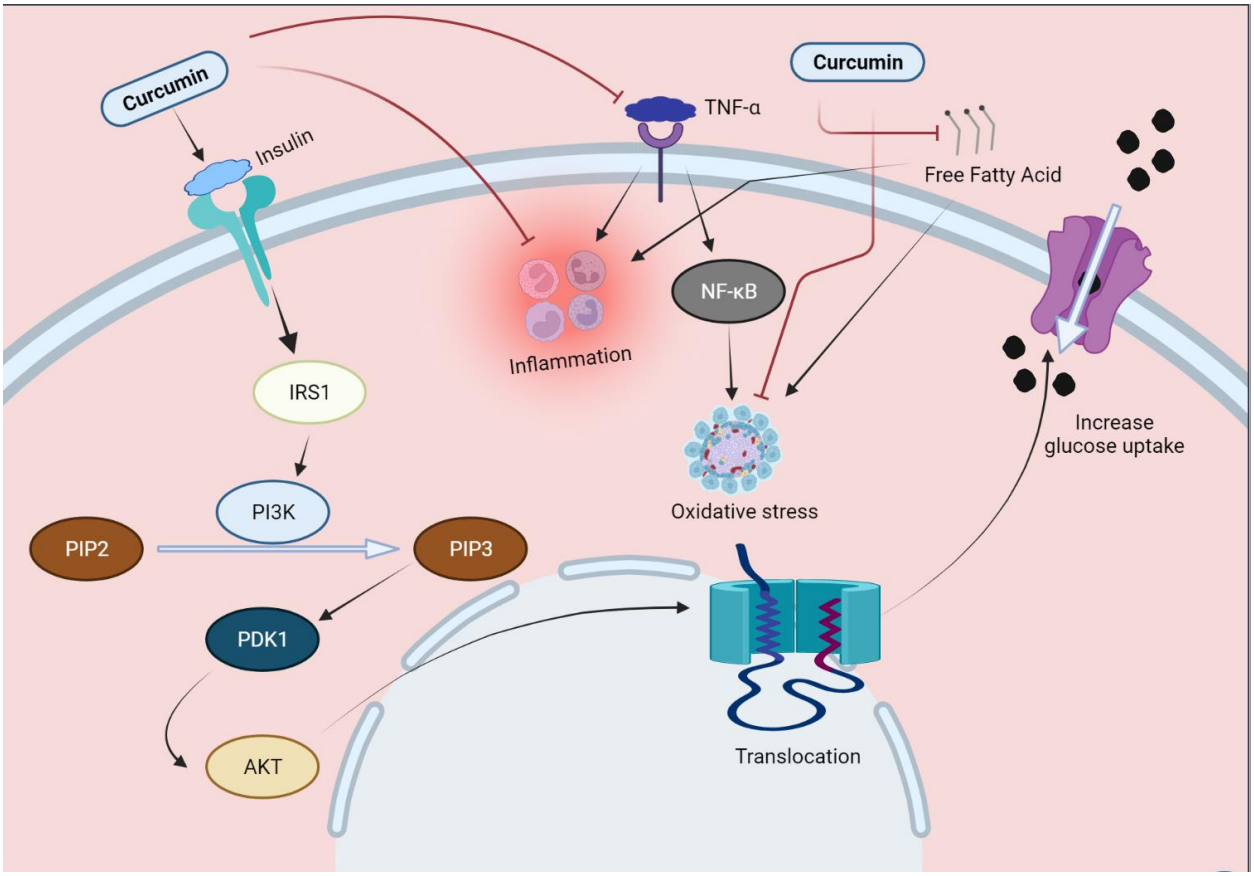

Figure 4: Curcumin effect on oxidative stress, inflammatory mediators and its cellular effects. Activation of tissue necrosis factor leads to induction of oxidative stress and inflammation while excessive fatty acid leads to induction of oxidative stress. Curcumin act on both free fatty acid and tissue necrosis factors leads to inhibition of inflammation and oxidative stress state. Abbreviations: TNF-α: tumor necrosis factor- α; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; IRS1: insulin receptor substrate 1; AKT: protein kinase B.

diabetes resistance management. Insulin resistance has a prominent connection with diabetes resistance that was managed by curcumin through reduction in the expression of SOCS3, STAT3 signaling, increasing level of IRS – 1, Rac –1 and suppression of phosphorylation of ERK/JNK signaling pathway. Taken together, curcumin has displayed a versatile role in the management of diabetes mellitus by attenuating oxidative stress mediators. Curcumin metabolites have shown significant results in diabetes mellitus treatment focusing oxidative stress thus there is need for future investigations to explore.

The structural – activity relationship of curcumin to develop new curcumin agents in this context that are more effective than natural curcumin. Curcumin due to its low bioavailability have been evaluated from nano platform and very few studies are available in targeting oxidative stress mediators induced diabetes mellitus. Future studies are required in this regard and their respective clinical trials as well. Resistant diabetes has also been less explored and less evaluated for targeting oxidative stress because determining total antioxidant capacity or activity is not sufficient and valid for such a big dilemma. In a nutshell, further explorations in the discussed issues can open new avenues for curcumin delivery in diabetes mellitus and surely will lessen the burden of diabetes related complications.

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