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Modulatory effect of caffeic acid in alleviating diabetes and associated complications

Caffeic acid and diabetes associated complications

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Abstract

Diabetes Mellitus (DM) is one of the most common metabolic disorders characterized by elevated blood glucose levels. Prolonged uncontrolled hyperglycemia often leads to multi organ damage including diabetic neuropathy, nephropathy, retinopathy, cardiovascular disorders, and diabetic foot ulcers. Excess production of free radicals causing oxidative stress in tissues is often considered to be the primary cause of onset and progression of DM and associated complications. Natural polyphenols can be used to induce or inhibit the expression of antioxidant enzymes that include superoxide dismutase, catalase, glutathione peroxidase andheme oxygenase-1, that are essential in maintaining redox balance, and ameliorate oxidative stress. Caffeic acid (CA) is a polyphenol, derived from hydroxycinnamic acid, and possesses numerous physiological properties including antioxidant, anti-inflammatory, anti-atherosclerotic, immune-stimulatory, cardioprotective, antiproliferative, and hepatoprotective activities. CA acts as a regulatory compound affecting numerous biochemical pathways and multiple targets. These include numerous transcription factors such as nuclear factor-κB, tumor necrosis factor-α, interleukin-6, cyclooxygenase-2 and nuclear factor erythroid 2-related factor 2. Therefore, this review summarizes the pharmacological properties, molecular mechanisms and pharmacokinetic profile of CA in mitigating the adverse effects of DM and associated complications. The bioavailability, drug delivery and clinical trials of CA have also been discussed.

Key Words: Diabetes mellitus; caffeic acid; diabetic foot ulcer; retinopathy; nephropathy

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Core Tip: Diabetes mellitus has emerged as one of the most common metabolic disorders worldwide which can lead to other complications such as retinopathy,

nephropathy, neuropathy and foot ulcers. Free radical induced oxidative stress is one of the primary factors causing diabetes. Caffeic acid is a natural polyphenol obtained from various fruits and vegetables. Caffeic acid and its derivatives act as an antioxidant and regulate the signalling pathways involved in lipid and carbohydrate metabolism. Caffeic acid also exerts anti diabetic effects by modulation of inflammatory cytokines and transcription factors.

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder marked by elevated blood sugar levels that stems from the complete loss or dysfunction of insulin producing pancreatic β-cells which subsequently result in other complications in several organs of the body.DM is one of the most frequently occurring metabolic diseases worldwide and is the leading causes of death due to comorbidities [1,2]. The main subtypes of DM are type 1 diabetes (T1DM) and type 2 diabetes (T2DM). T1DM, also referred to as insulin dependent DM, is an autoimmune condition that is mediated by the dysfunction of pancreatic β -cells with complete loss of insulin production [3]. T2DM is the insulin resistance (IR) type that occurs when pancreatic β-cells are incapable of producing enough insulin resulting in hyperglycemia. T2DM affects 90–95% of diabetic individuals globally [4]. Several reports suggest that around 400 million people worldwide would be affected by DM by the year 2025 [5]. Both types of DM are frequently linked to long-term consequences such as higher risk of cardiovascular diseases (CVD), retinopathy, neuropathy, nephropathy, foot ulcers, and other vascular anomalies. These complications consequently lead to blindness in diabetic patients, end-stage renal disease, atherosclerosis and even mortality [6]. Compared to non-diabetic individuals, T2DM patients are at much higher risk of foot injuries and cardiovascular morbidity like atherosclerosis [7]. Studies have demonstrated that metabolic variables, oxidation/glucoxidation, and changes in vascular reactivity are some of the major factors that contribute to diabetic atherosclerosis [8]. Although the pathophysiological mechanism linking DM to its complications is yet to be extensively explored, oxidative stress appears to be a key

factor [9–11]. Several reports have suggested that increased oxidative/nitrosative stress and cellular redox disturbances facilitate the etiology and development of both T1DM and T2DM. Uncontrolled hyperglycemia causes oxidative stress and further damages the cells primarily by targeting various metabolic pathways such as enhancement of polyol pathway, increased synthesis of advanced glycation end products (AGEs), activation of protein kinase C, and upregulated hexosamine pathway [9, 10]. Therefore, hyperglycemia results in elevated levels of reactive oxygen species (ROS) and reactive nitrogen species (RNS) in majority of organs. Moreover, a decrease in cellular antioxidant defences is linked to an increase in oxidative stress in diabetic individuals [9, 12, 13]. The primary factor contributing to endothelial cell failure in diabetic complications may be due to increased lipid peroxidation caused by oxidative stress. Endothelial dysfunction in DM has been attributed to excessive generation and/or insufficient clearance of free radicals by the antioxidant defence system [14] (**Figure 1**). Since oxidative stress is effective in the development of T1DM, T2DM, and diabetes associated complications, use of antioxidants as a counter measure could be beneficial. When cells are exposed to chemicals/oxidants, natural polyphenols can be used to induce or inhibit the expression of enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and heme oxygenase-1 (HO-1) that are essential in maintaining cellular homeostasis [15]. Natural polyphenols are secondary metabolites having lower risk of adverse effects when employed in conventional and alternative medicine[16].

Caffeic acid (CA) is a polyphenolic derivative of hydroxycinnamic acid,formed as a product of secondary metabolism in fruits and vegetables [17-19]. CA can be present in simple monomeric form as amides, glycosides, sugar andorganic acid esters, or in complex oligomeric forms as derivatives of flavonoids.CA can also be found attached to some cell wall proteins and polymers [19-20]. CA inhibits the growth of bacteria, fungi, and insects, protects plantsfrom UV-B radiations, and contributes to plants' defensive mechanism against predators, pests, and illnesses [21]. Numerous biological effects of CA and its derivatives have been demonstrated through experimentalstudies, including

antibacterial, antiviral, antioxidant, anti-inflammatory, anti-atherosclerotic, immune-stimulatory, cardioprotective, antiproliferative, and hepatoprotective activities [21-25]. Propolis, derived from honeybee is rich in caffeic acid phenethyl ester (CAPE), a common naturally occurring derivative of CA having widespread applications in research and industry [26]. CAPE acts as a regulatory compound affecting numerous biochemical pathways and multiple intracellular targets including several transcription factors viz., nuclear factor-κB (NF-κB), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), cyclooxygenase-2 (COX-2), nuclear factor erythroid 2-related factor 2 (Nrf-2), inducible nitric oxide synthase (iNOS), activated T-cell nuclear factor (NFat), and hypoxia-inducible factor-1 (HIF-1) [26-30]. Most of these pathways are usually involved in the regulation of inflammatory and oxidative stress markers. Numerous studies have reported the efficacy of CAPE in the treatment of stress-induced pathologies. Recent studies have shown the protective ability of CAPE on nephrotoxicity induced by a number of xenobiotics (methotrexate, doxorubicin, cisplatin, toluene, carbon tetrachloride, *etc.*) or by diverse toxic conditions [31]. Several reports suggest the application of CAPE in experimental and clinical studies for the treatment of several diseases such as cancer, thyroid, liver diseases, hepatic insulin resistance, non-alcoholic fatty liver disease or hepatocellular carcinoma [32, 33]. *In vivo* studies have reported that oral ingestion of CAPE stalled the progression of atherosclerosis in mice deficient in apolipoprotein E [32]. In addition, involvement of CAPE in molecular signalling pathways suggests that CAPE has therapeutic efficacy in diverse inflammatory diseases and cancer [31-32]. Similarly, CA treatment has also exhibited protective efficacy in various organs such as brain, kidney, lung, ovaries and heart from diabetes induced damage [34-36]. Therefore, this review reports the structural and pharmacological properties of CA and its derivatives with special emphasis on the key mechanisms of action and pharmacokinetic properties of CA, especially in DM and associated complications.

SOURCES AND CHEMISTRY OF CAFFEIC ACID

CA occurs naturally in several vegetables and fruits including kiwis, blueberries, plums, cherries, apples, cereals, carrots, and cabbage. CA can also be found in propolis, which is a resinous substance made by honeybees [37]. Different plant species have variable amounts of CA [38]. It is a very prevalent phenolic acid that accounts for 75 to100 percent of the total hydroxycinnamic acid in fruits [39]. Structurally, CA is a phenylalanine derived hydroxycinnamic acid with a 3,4-dihydroxyaromatic ring connected to carboxyl group through a trans-ethylene bond [37]. CA is synthesized naturally in plants *via* the endogenous shikimate pathway[23, 37]. The biosynthesis of CA begins with precursor shikimic acid and involves three enzymatic reactions: 1) phosphorylation shikimate kinase; 2) the conjugation of phosphoenolpyruvate 5-enolpyruvylshikimate-3-phosphate (EPSP) synthase; and 3) formation of intermediary metabolite chorismic acid by the enzyme chorismate synthase [23, 37]. Cinnamic acid is produced from the deamination of L-phenylalanine by enzyme phenylalanine ammonia lyase (PAL); it is converted into p-coumaric acid by the action of cinnamate-4-hydroxylase (C4H) which is subsequently converted into CA by enzyme 4-coumarate 3-hydroxylase (C3H) [23] (**Figure 2**). CA is generally extracted from plant materials and by microbial synthesis using organisms like *Escherichia coli*. Two enzymes can be produced by genetic modifications in *E. coli* strains: tyrosine ammonia lyase (TAL) and 3-hydroxylase hydroxyphenylacetate (4HPA3H) which act on L-tyrosine to produce L-dopa and coumaric acid, respectively leading to the synthesis of CA [36].

PHARMACOKINETICS OF CAFFEIC ACID

CA has a molecular weight of 180.16 g/mol and is typically found as a white, amorphous powder. The partition coefficient (logP) for CA ranges from 1 to 1.3 [40, 41]. In addition, propolis contains large amounts of naturally occurring derivative of CA, the CAPE that appears as a white crystalline solid and has a molecular weight of 284.31 g/mol. The intriguing aspect of CAPE is its ability to traverse the blood-brain barrier, which can be attributed to logP values of CAPE ranging between 3.2-13.8 [41-43]. CA is essentially found in food in esterified form with chlorogenic acid, thus limiting its

absorption in the body [44]. Human tissues such as the intestinal mucosa,stomach, liver, and biological fluids such as plasma, duodenal fluid, and gastric juice lack the esterase enzymes that hydrolyze chlorogenic acid to release CA. Thus, it is hydrolyzed by intestinal microflora before its absorption [42, 44]. As a result, the pharmacokinetic process starts when CA is consumed and enters the stomach in its esterified state, where a small amount of CA is absorbed [41-44]. Thereafter, the intestinal mucosa absorbs up to 95% CA in its free form after the bacterial esterases in the colon break the ester part of CA [42-44]. Monocarboxylic acid transporters are involved in the active transport of CA across membranes into intestinal cells [36, 42, 44]. The peak plasma concentration of CA occurs after 1 h of meal digestion, and it takes repeated dosage every 2 h to sustain high levels of CA in plasma [36, 42]. Under anaerobic conditions, gut bacteria having tyrosine decarboxylase can cause decarboxylation of CA producing a compound known as 3-(3-hydroxyphenyl)-propionic acid that has stronger antioxidant activity than CA [45]. Sulfotransferases, UDP-glucuronosyltransferases, and catechol-o-methyltransferases catalyze three main enzymatic conjugation processes of sulphation, glucuronidation and methylation of CA, respectively that occur immediately after absorption. This increases the hydrophilic properties of CA thus reducing its toxicity and speeding up elimination. The liver and kidney are the major sites of CA metabolism. The primary elimination route of CA (5.9% to 27%) is *via* urine [43-45].

ANTI-DIABETIC EFFECTS OF CAFFEIC ACID

DM is characterized by hyperglycemia, altered lipid and carbohydrate metabolism, and oxidative stress [1, 2, 46]. The successful control of high blood sugar levels with natural polyphenols may be significant in minimizing diabetic complications, particularly micro- and macrovascular disorders. Plant products used in traditional medicine constitute a potential alternative for effective control of diabetes, owing to their affordability, high efficacy, and minimal negative effects, [47, 48, 49]. CA is a natural compound that is known to promote insulin secretion, inhibit α-amylase and β-glucosidase, prevent sodium-dependent glucose transporter-1 from absorbing glucose

in the gut, and lowers hepatic glucose output. Besides its anti-diabetic efficacy, CA also modifies the microbiome, facilitates insulin-dependent glucose uptake, activate adenosine monophosphate-activated protein kinase, and have immunomodulatory, antimicrobial, hypocholesteremic and antioxidant properties [36, 49]. Experimentally, in streptozotocin (STZ) induced diabetic rats, and Balb/c and C57BL/KsJ-db/db mice, CA exhibited potential antihyperglycemic effects along with antioxidant and anti-inflammatory properties [50, 51]. CA may exert its protective effects by activating and safeguarding intracellular antioxidant enzymes, and by transferring hydrogen atoms, single electrons, as well as by chelating metal ions [52]. In addition, CA helps to upregulate the transcription factor NrF2 which controls the expression of over 200 genes involved in the cellular antioxidant and immune regulatory mechanism by binding with antioxidant response elements, which is also linked with the detoxification of xenobiotics. CA also regulates β-cell and adipocyte GLUT4 functions, increases activity of glucokinase in hepatocytes, inhibits glucose-6 phosphatase and phosphoenolpyruvate carboxykinase, and reduces glycosylated haemoglobin, thus resulting in controlled DM. CA aids in enhancing the utilization of glucose and glycogen synthases. This leads to reduced cholesterol biosynthesis and prevention of lipogenesis. CA suppresses iron-induced elevation of cholesterol and improves the levels of plasma insulin, C-peptide and leptin [53]. In a study with STZ-induced diabetic rats, a significant decrease in MDA level and SOD and CAT activities was observed in liver, retina, and heart post CA treatment. Insulin-like growth factors (IGFs) are known to be associated with the progression of DM where reduced serum IGF-I levels have been linked with poor glycemic control in DM, while elevated plasma IGF-II levels have been linked to the progression of DM [54, 55]. In STZ-induced diabetic rats, the effects of CA administration led to amelioration of changes in gene expression as well as changes in the levels of IGF-I and IGF-II in the blood, liver, heart, and kidney [35, 56].

ROLE OF CAFFEIC ACID IN DIABETES ASSOCIATED COMPLICATIONS

Diabetic foot and wound healing

Chronic wounds below the ankle or foot lesions in diabetic patients that penetrate the dermis layer are known as diabetic foot ulcers (DFU) [57]. People with diabetes have a lifetime risk of developing foot ulcers in 25% cases which may lead to 50–70% of total nontraumatic amputations [58-61]. In recent years, amputation rates have increased significantly which in turn has raised the rate of morbidity and death [62-65]. The wound healing cascade in diabetic patients is often hindered and delayed due to high blood sugar levels [66]. Hyperglycemia leads to a series of events such as formation of AGEs, nonenzymatic glycosylation, activation of the polyol pathway, the diacylglycerol-(DAG) protein kinase C pathway, and hyperactivity of the hexosamine pathway [67, 68]. These alterations are linked to a prolonged inflammatory phase causing stiffening of endothelial walls, which makes it challenging for blood to pass *via* tiny arteries near the surface of the incision [69]. As a result, there is also lack of oxygen release and nutrition at the wound site causing further elevation of blood sugar levels in the wound area. Therefore, the wound healing cascade is prolonged, leukocyte migration is reduced, and macrophage introduction is delayed [70]. Additionally, hyperglycemia also activates an inflammatory reaction by triggering nuclear factor-kappa (NF-K) light-chain-enhancer of activated B cells [71, 72]. Moreover, oxidative stress, dyslipidemia, and insulin resistance play a significant role in the development of DFU [73, 74]. Thus, management of all these factors is crucial for the treatment of DFU.

Studies have shown that low glycemic index of CA and its derivatives is mainly responsible for their antidiabetic, antioxidant, and anti-inflammatory properties which aids in managing foot ulcers [75-78]. An early study on STZ induced diabetic mice revealed that topical administration of propolis is well tolerated and aids in healing of human DFUs [79]. CAPE increases wound contraction and re-epithelialization by reducing oxidative stress and accelerates cutaneous wound healing mediated by its antioxidant action [80, 81]. In another study on diabetic mice, topical application of propolis was found to stimulate the release of VEGF in smooth muscle cells and facilitated the relaxation of arteries *via* the nitric oxide (NO)/cyclic guanosine

monophosphate (cGMP) pathway which accelerated the healing of cutaneous diabetic wounds in mice [82, 83] (**Figure 3**) (**Table 1**).

Diabetic Nephropathy

Diabetic nephropathy is a consequence of prolonged uncontrolled DM causing damage to the renal blood vessel clusters. The pathogenesis of diabetic nephropathy and other complications of diabetes have been linked to non-enzymatic glycation, with the formation of AGEs, also recognized as Maillard reaction products. These AGEs include glycated haemoglobin, glycated albumin, pentosidine, and carboxymethyllysine (CML) [84-86]. In addition, disruption in Th1-Th2 cytokine balance, and over production of pro-inflammatory cytokines results in increased inflammatory stress in diabetic patients which further accelerates diabetic nephropathy [87, 88]. Early investigations have suggested that CA lowers blood glucose by modulating the polyol pathway. Aldose reductase (AR) is the first and rate-limiting enzyme in the polyol pathway that reduces glucose to sorbitol, which could be further metabolised to fructose by the enzyme sorbitol dehydrogenase (SDH)[89, 90]. The generation of AGEs was increased by the flux through SDH and an elevated fructose level, which enhanced diabetes-induced microvascular abnormalities [91] (**Figure 4**). In diabetic mice, CA significantly decreased the production of AGEs, inflammatory cytokines like IL-1b and IL-6, levels of plasma HbA1c, urinary glycated albumin, renal CML, pentosidine, sorbitol and fructose, and considerably reduced the activity of renal AR and SDH along with suppression of renal AR mRNA expression [92]. In an *in vivo* study with STZ-induced diabetic rats, CA in a dose range of 10-50 mg/kg attenuated diabetic nephropathy *via* modulation of autophagy pathway by inhibiting autophagy regulating miRNAs [93]. In another study on STZ-induced diabetic rats, oral treatment of CA at 40 mg/kg mitigated renal damage and significantly reduced fasting blood glucose, cholesterol and triglyceride in diabetic rats. CA treatment also improved histological parameters in the diabetic kidney and downregulated the expression of miR-636 [94]. Another study in STZ-induced diabetic mice, intraperitoneal treatment with CA derivatives CAPE and caffeic acid para-nitro

phenethyl ester (CAPE-*p*NO_2) at 20 µmol/kg/day demonstrated improved renal biochemical parameters such as decreased serum creatinine, MDA, 24-h albumin excretion, blood urea nitrogen, myeloperoxidase levels and SOD activity in diabetic mice. CAPE and CAPE-*p*NO_2 also inhibited inflammation *via* the Akt/NF-κB pathway and prevented nephropathy through the transforming growth factor-β (TGF-β)/Smad pathway [95] (**Table 1**).

Diabetic Retinopathy

Long term DM results in diabetic retinopathy characterised by aberrant retinal blood vessel proliferation and microvascular retinal alterations, resulting in partial vision loss or even complete blindness. One of the major factors causing diabetic retinopathy is VEGF driven angiogenesis. In a study using human umbilical vein endothelial cells (HUVECs), CAPE treatment in the dose range of 3-10 µM decreased VEGF-induced angiogenesis indicating possible positive effects in the treatment of diabetic retinopathy [96] (**Figure 4**). In another study, HUVECs treated with CAPE at 5-20 µg/mL exhibited reduction of VEGF-induced neovascularization and proliferation, tube formation, and migration. The protective efficacy of CAPE can be attributed to the inhibition of VEGF-induced VEGF receptor-2 (VEGRF-2) activation and associated downstream pathways [97]. An *in vivo* study in STZ-induced diabetic rat model demonstrated the protective efficacy of caffeic acid hexyl (CAF6) and dodecyl (CAF12) amide derivatives in diabetic retinopathy. Treatment with CAF6 and CAF12 at a dose of 250 mmol/L led to increased retinal SOD levels, and improved thickness of the whole retinal layer, outer nuclear layer, and ganglion cell count. The CA derivatives ameliorated diabetic retinopathy *via* modulation of extracellular signal regulated kinase (ERK)1/2 and protein kinase-B/Akt signalling pathways [98] (**Table 1**).

Diabetic Neuropathy and Cardiovascular Complications

Brain is another organ which is adversely affected by prolonged uncontrolled hypergycemia, and cerebral dysfunction in diabetic patients is known to be a

multifactorial process [99]. Free radical mediated oxidative stress induced by hyperglycemia plays an important role in the pathogenesis of diabetic neuropathy [100]. It stimulates the production of inflammatory cytokine TNF-α and promotes the expression of NF-ƙ B [101]. The NO radical in the central nervous system acts as an important regulator leading to the generation of RNS *via* enzyme iNOS and results in elevated oxidative stress in brain. In an *in vivo* study, STZ-induced diabetic rats post intraperitoneal treatment with CAPE at a dose of 10 µM/kg/day showed reduced NO radical, lipid peroxidation, and increased activities of antioxidant enzymes such as SOD, CAT and GSH-Px in rat brain. In addition, CAPE was shown to inhibit the activity of iNOS enzyme, thus preventing excess production of RNS [102].

Hyperglycemia combined with dyslipidemia, oxidative stress, and inflammation cause CVD such as hypertension, cardiac myopathy and atherosclerosis. DM mediated CVD is characterized by elevated levels of triacylglycerol (TG), low density lipoprotein (LDL), very low-density lipoprotein (VLDL) and total cholesterol (TC). Atherogenic dyslipidemia in diabetic patients leads to increased risk of cardiac failure. Studies on alloxan induced diabetic mice have revealed that CA at a dose of 50 mg/kg acts as a potent agent in controlling hypergycemia and reduced atherogenic indices such as TG, LDL-c, VLDL-c and TC. Thus, successful restoration of lipid and glucose metabolism parameters in mice by intraperitoneal CA administration led to improved cardiac function [53]. In another study, diabetic mice when orally fed with 2% CA, exhibited improved glycemic control and lipid metabolism. CA treatment led to significant increase in plasma antithrombin-III and protein C activities, and decrease in MDA, IL-β, IL-6, TNF-α levels [34]. Studies on a STZ-induced T1DM rat model demonstrated that intraperitoneal pre-treatment with caffeic acid phenethyl amide (CAPA) at doses 3 and 15 mg/kg led to reduced myocardial infarction and amelioration of cardiac dysfunction [103] (**Table 1**).

BIOAVAILABILITY AND DRUG DELIVERY OF CAFFEIC ACID

Plant derived natural products including CA have several applications in the treatment of a wide range of diseases. However, there are many limitations that come in the way of using phytochemicals as alternative medicine. To ascertain the optimum utilization of plant derived compounds in clinical investigations, it is important to design novel carriers for the delivery of natural products [104, 105]. The use of CA as a pharmaceutical is constrained by a number of physicochemical and pharmacokinetic factors including poor water solubility, and lack of specific tissue targeting [106]. Studies have also shown that CA has low oral bioavailability (14.7%) and low intestinal absorption (12.4%) in rat model [107]. Therefore, numerous nanoparticles (NPs) have been created for the delivery of CA and related compounds in disease therapy with positive outcomes including polymeric NPs, metal NPs, carbon nanomaterials, and lipid nanostructures [108, 109]. The use of NPs for targeted delivery of CA is well reported. The combinations of gold and iron NPs (Au-Fe3O4) with CA, quercetin, and 5-fluorocytidine have been formulated for use in breast cancer treatment. Studies related with formulation and development of CA-NPs are mostly targeted for cancer therapy. The release of quercetin and CA from these nanostructures inhibits lactate secretion and prevents glycolytic reprogramming [106, 107]. Additionally, NPs have also been designed for CAPE delivery for the treatment of cancer. In a recent study, methoxy poly (ethylene glycol)-b-poly(-caprolactone) (CE) was used to create polymeric nanostructures, which were subsequently loaded with CAPE [45, 110, 111]. There is still much work to be done in terms of NP formulation and design. Hence, further studies are required to examine the potential functions of NPs of CA for better delivery, in treatment of other diseases including DM.

CLINICAL TRIALS AND FUTURE PROSPECTS

Phytometabolites are pharmacologically active compounds and their clinical applications are constantly increasing [45, 112, 113]. Several reports have shown that approximately one fourth of all clinical compounds used as drugs are derived from natural products[114, 115]. The pharmacological action of CA and its derivatives, particularly CAPE, as hepatoprotective, reno-protective, antioxidant, anti-diabetic, anti-

inflammatory and anticancer agents has been well documented. The activity of antioxidant enzymes such as SOD, CAT, HO-1 is positively modulated by CA. CAPE treatment leads to protection against oxidative stress mediated diabetic complications by regulating the transcription factors NF-κB, Nrf2, COX-2, and associated molecular pathways. Moreover, CAPE shows notable efficacy in both *in vitro* and *in vivo* diabetic models with no substantial negative effects. CA exerts anti-diabetic efficacy *in vitro* and *in vivo* via reduced VEGF angiogenesis, decreased MDA, TNF-α, IL-β, IL-6, and other inflammatory and oxidative stress markers.

In order to examine the clinical trials' data with respect to CA and related compounds in diabetic patients, we searched on the largest clinical trial database at 'https://clinicaltrials.gov'. No search results were obtained with the keywords 'CA/CAPE and diabetes'. Since propolis found in beehive is a major source of CAPE, therefore we searched with keywords 'propolis and diabetes' on the database. Three studies were found in which propolis was administered orally or applied topically to diabetic patients. The results have been summarized in **Table 2**.

CA has potential application in the treatment of several diseases including diabetes and associated complications. However, more *in vivo* research needs to be done for a better understanding of the mode of action of CA in DM and associated problems, particularly the role of cytoprotective enzymes like HO-1. Additionally, pharmacokinetic studies are required to entirely understand the metabolic pathway of CA post oral administration. Thus, further clinical investigations in humans are needed to determine the pharmacological potential of CA in major illnesses like diabetes.

CONCLUSION

DM has emerged as one of the most common metabolic disorders worldwide which can lead to other complications such as retinopathy, nephropathy, neuropathy and foot ulcers. Free radical induced oxidative stress is one of the primary factors causing DM.

CA is a natural polyphenol obtained from various fruits and vegetables. CA and its derivatives act as an antioxidant to regulate the signalling pathways involved in lipid and carbohydrate metabolism. CA also exerts anti diabetic effects by modulation of inflammatory cytokines and transcription factors. Furthermore, novel delivery strategies are being used for transport of CA to enhance its bioavailability, which has enabled the widespread use of CA in various disease therapies.

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