REVIEW
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Therapeutic Potential of Cannabis Plant in Diabetes

ABSTRACT

Diabetes mellitus (DM) is a metabolic disorder of the endocrine system that poses a serious threat to human health. Although many chemical substances are available for the prevention and treatment of DM and its complications, an optimal treatment for diabetes is not yet available. As an alternative to these synthetic substances, plants are widely used in various traditional medicine systems for the prevention of diabetes. *Cannabis sativa* L., a member of the Cannabaceae family, is one of the plants with very ancient medicinal use. More than 100 phytocannabinoids have been identified in *C. sativa*, most notably Δ9-tetrahydrocannabinol and cannabidiol. In addition to cannabinoids, cannabis also contains terpenoids and flavonoids. Various studies have shown that these compounds have many therapeutic effects such as antioxidant, analgesic, immunomodulatory, and anticonvulsant. This review provides an overview of the therapeutic effects of the cannabis plant and its constituents on diabetes and its complications.

Keywords: Cannabinoid, *Cannabis sativa* L, diabetes, endocannabinoid system

What is already known on this topic?

- Diabetes mellitus (DM), a major metabolic disease, is on the rise.
- There are many plant species used as complementary or alternative therapy in the treatment of DM.
- It is known that the cannabis plant has been used for medicinal purposes since ancient times.

What does this study add on this topic?

- This study is a review of the effects of the cannabis plant in the treatment of DM and its complications.
- It could be useful in paving the way for the cultivation of cannabis, which is currently banned in the country.

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease characterized by high blood glucose levels due to insufficient insulin secretion and insulin resistance. The most common type, type 2 diabetes, usually occurs in adults and occurs when the body becomes resistant to insulin or does not produce enough insulin. Type 1 diabetes, also known as insulin-dependent diabetes, is a chronic condition in which the pancreas produces little or no insulin.[1] In 2021, approximately 537 million adults aged 20-79 years were reported to have DM worldwide, and this number is projected to increase by 46% to 783 million by 2045.[2] If diabetes is not controlled, it can lead to serious complications in the heart, blood vessels, eyes, kidneys, and nerves.[3] The use of medicinal plants and/or herbal products as complementary/alternative medicine treatment strategies for people with diabetes is attracting interest as a new approach to managing other treatments and complications of diabetes.[4,5]

The medicinal use of the cannabis plant dates back thousands of years. Originally used as fiber and grain, the first use of cannabis as a medicine. It is thought to have been used by the Chinese emperor Chen Nung, who lived around 2700 BC. The medical use of cannabis began in Asia and entered Western medicine in the mid-19th century.[6,7] In the last few decades, there has been intense interest in cannabis and its active ingredients due to its therapeutic effect on various diseases.[8,9] Decriminalizing and legalizing cannabis use, which is currently banned in the country, will make it easier to research the therapeutic effects of cannabis. This review aims to examine the therapeutic effects of the cannabis plant and its constituents on diabetes and its complications.

HISTORY OF CANNABIS, TRADITIONAL USES, DISTRIBUTION, AND CULTIVATION

The cannabis plant (hemp), a member of the Cannabaceae family, dates back to the earliest agricultural human societies in Asia. *Cannabis*, an annual, dicotyledonous, herbaceous, and fast-growing plant, usually grows in temperate

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climates and varies in height from 1 to 3 meters. The plant's stem is erect and hollow, with thorny hairs, while its leaves are usually palmate, deeply toothed, and green in color.[10] Although the cannabis plant is mostly dioecious (male and female individuals are separate), some monoecious individuals can be seen. The flowering period of the plant depends on the photoperiod (day length) and the flowering period is usually 8-12 weeks, depending on the species and environmental conditions. Pollination is by wind.[11,12]

The cannabis plant has several uses. The stems of the plant, which are rich in fibers, are used for yarn, weaving, and fabric production, while the pulpy part of the plant is used for paper production. Hemp oil (not to be confused with cannabis oil) and hemp protein from hemp seeds can be consumed as food.[13] The plant contains chemicals such as cannabinoids (CBs), terpenoids, flavonoids, and alkaloids.[14] The most potent compounds are CBs, which belong to the class of terpenophenolic compounds and are usually found in the trichome spaces of female flowers.[15,16]

There are 3 main known species of the cannabis plant: *C. sativa*, *Cannabis indica*, and *Cannabis ruderalis*. The *C. sativa* type is generally taller, thinner-leaved, and late flowering compared to other types. Although known for its stimulating effects, it is usually high in tetrahydrocannabinol (THC). The *C. indica* type is shorter, wider-leaved, and earlier flowering; it has a high cannabidiol (CBD) content and has sedative effects. The *C. ruderalis* type is short and has small leaves; it begins to flower when it reaches a certain age, regardless of the length of the day (auto-flowering). For this reason, it is often used in modern hybrids. The CB ratios contained in the different types and subspecies allow them to be selected according to their intended use.[11]

CANNABINOIDS

Cannabinoids are divided into 2 groups: endogenous CBss (endocannabinoids (eCBs)) and exogenous CBs. Endocannabinoids are lipid-based messengers naturally derived from lipid precursors in plasma membranes. They are also part of the eCB system.[17] Exogenous CBs include synthetic CBs and phytocannabinoids produced outside the body.[18] Synthetic CBs are laboratory-produced compounds that mimic the structure and function of phytocannabinoids. These compounds include both FDA-approved drugs (dronabinol and nabilone) and illicitly manufactured CBs.[18,19] Phytocannabinoids are natural CBs derived from the cannabis plant and are of interest for their potential pharmacological effects and medical uses. The number of CB and non-CB bioactive compounds identified in cannabis is reported to be over 585, of which over 100 are phytocannabinoids. The THC (the 2 main compounds Δ8-THC and Δ9-THC) and CBD are the most studied phytocannabinoids.[20-22] Both synthetic and naturally occurring phytocannabinoids interact with the eCB system (Figure 1).[23]

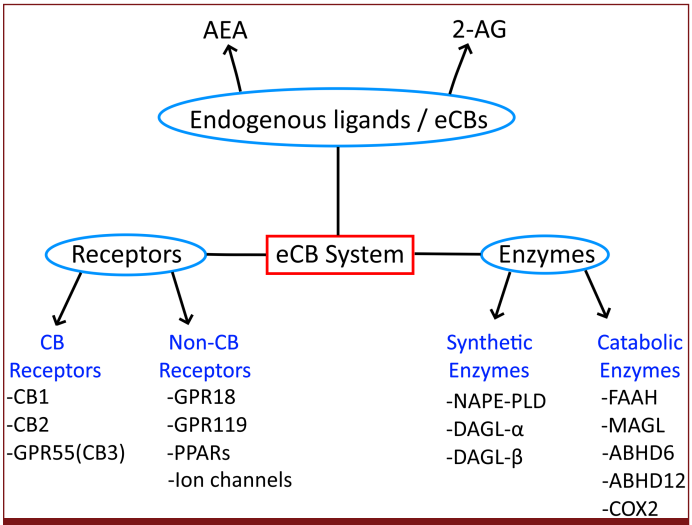

Figure 1. The endocannabinoid (eCB) system consists of 3 main components: 2-AG (2-arachidonoylglycerol), ABHD6 (α/β-hydrolase domain-containing 6, AEA; anandamide, CB; cannabinoid receptor, COX2; cyclooxygenase-2, DAGL; diacylglycerol lipase, FAAH; fatty acid amide hydrolase), GPR55 (G protein-coupled receptor 55, MAGL; monoacylglycerol lipase, PPAR; peroxisome-proliferator-activated receptors.

ENDOCANNABINOIS SYSTEM

The eCB system, a lipid messenger system, consists of CB receptors, their endogenous ligands (eCBs), and enzymes that regulate the biosynthesis and degradation of eCBs.[24,25] The G protein-coupled receptors CB1 and CB2 are the most well-known CB receptors. G protein-coupled receptor 55 (GPR55) is considered a potential candidate for a third CB receptor.[26] The naturally occurring eCBs that activate CB receptors are N-arachidonoylethanolamine (anandamide/AEA) and 2-arachidonoylglycerol (2-AG).[27,28] The precursors of these eCBs are found in lipid membranes. Endogenous AEA synthesis occurs in 2 steps: first, the formation of N-arachidonoyl phosphatidylethanolamine (NAPE) by the transfer of arachidonic acid from phosphatidylcholine to phosphatidylethanolamine, and then the formation of AEA by the cleavage of NAPE by NAPE phospholipase D. The synthesis of 2-AG is the lipase-catalyzed conversion of diacylglycerol produced from membrane phospholipids to 2-AG.[29] The eCB signalling is regulated by metabolic enzymes such as fatty acid amide hydrolase (FAAH), which degrades AEA, and monoacylglycerol lipase (MAGL), which hydrolyses 2-AG. In addition to these enzymes, FAAH-2, N-acylethanolamine-hydrolyzing acid amidase (NAAA), alpha/beta-hydrolase, cyclooxygenase-2 (COX-2), and cytochrome P450 have also been reported to play roles in the hydrolysis of AEA and 2-AG (Figure 2).[30,31] The eCB system has been expanded with the discovery of the eCB-like molecules palmitoylethanolamide and oleoylethanolamide and other receptors, such as the peroxisome proliferator-activated receptor family.[32,33]

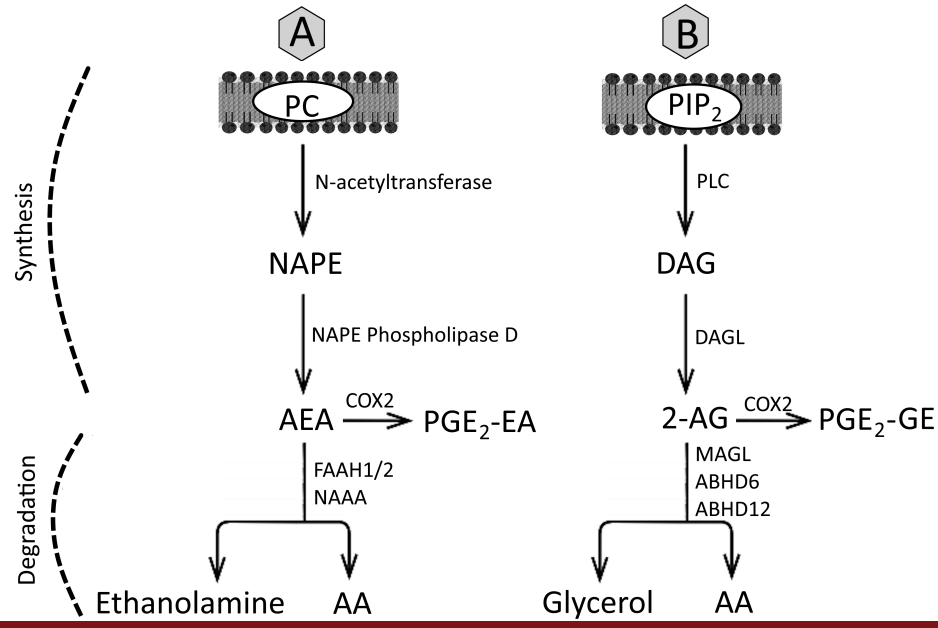

Figure 2. Synthesis and degradation of endocannabinoids. 2-AG, 2-arachidonylglycerol; AA, arachidonic acid; ABHD6, α/β-hydrolase domain-containing 6; AEA, anandamide; COX-2, cyclooxygenase-2; DAG, diacylglycerol; DAGL, diacylglycerol lipase; FAAH, fatty acid amide hydrolase; MAGL, monoacylglycerol lipase; NAAA, N-acylethanolamine hydrolyzing acid amidase; NAPE, N-acyl phosphatidylethanolamine; PC, phosphatidylcholine; PIP_2, phosphatidylinositol bis-phosphate; PGE 2-EA, prostaglandin E2-ethanolamine; PLC, phospholipase C.

THE RELATIONSHIP BETWEEN CANNABIS AND DIABETES AND ITS COMPLICATIONS

Many studies have shown that cannabis plants and their constituents may play a role in improving diabetes complications due to their various pharmacological effects. It has been reported that the administration of cannabis root juice and ethanol extracts in streptozotocin (STZ)-induced insulin-deficient diabetic mice improved glucose homeostasis and islet function, suppressed pancreatic β-cell apoptosis and cytokine-mediated inflammatory signaling. It has also been reported that these 2 extracts normalized insulin signaling defects in skeletal muscles and the STZ-induced apoptotic response in liver and kidney (Table 1).[34-36]

Cannabis and Diabetic Kidney Disease

Diabetic kidney disease (DKD), also known as diabetic nephropathy, is a serious complication of diabetes. The complication is a leading cause of renal failure.[37] The studies reported that CB1, CB2, and CB3 receptors are expressed in the kidney. These receptors have been reported to play important roles in kidney function and dysfunction.[38,39] Barutta et al[40] suggested that there is an imbalance between CB1 and CB2 receptors in DKD and that while protective CB2R signaling is impaired in the diabetic kidney, harmful CB1R signaling is increased, causing kidney damage by promoting oxidative stress, inflammation, and profibrotic processes. Bylan et al[41] reported in an in vivo study that hemp oil extract has protective effects against renal fibrosis, a major symptom of chronic kidney disease (CKD). In addition, it has been suggested that Δ9-THC, the main constituent of the cannabis plant, may be used as a therapeutic agent in CKD due to its ameliorative effects on the impaired redox status and immunomodulatory effects.[42] In contrast, a study in type 1 diabetic mice reported that although CBD treatment prevented glomerular hypertrophy and reduced T-cell infiltration, it significantly worsened overall kidney damage (Table 1).[43]

Cannabis and Diabetic Retinopathy

Diabetic retinopathy (DR) is a microvascular disease that affects about one-third of people with diabetes. The DR is the most common cause of severe vision loss in working-age adults and a leading cause of blindness worldwide. Hyperglycemia-induced inflammatory response and oxidative stress are known to play a role in the pathogenesis of DR.[44,45] Studies have shown that DR is associated with blood-retinal barrier dysfunction and neurotoxicity, and CBs may ameliorate oxidative stress and inflammation by providing neuroprotection.[46-48] It has been reported that treatment with CBD, a non-psychotropic CB, in STZ-induced diabetic rats reduced reactive oxygen species (ROS) production and prevented activation of the kinase MAP-p38. Thus, researchers have shown that the neuroprotective and protective effects of CBD treatment on the blood-retinal barrier may be related to its antioxidant and anti-inflammatory properties (Table 1).[46]

Cannabis and Diabetic Cardiomyopathy

Diabetic cardiomyopathy (DCM), a common cardiovascular complication of diabetes, is associated with high mortality. Oxidative stress and inflammation play an important role in the pathogenesis of DCM.[49,50] Rajesh

Table 1. The Effects of *Cannabis sativa* and Its Constituens in Diabetes Mellitus

Ref.	In vivo/In vitro Study	Concentration/Dosage	Duration	Effects
34	Streptozotocin (STZ)-induced diabetic C57BL/6J mice	*C. sativa* root water extract at 150 mg/kg/day *C. sativa* root ethanol extract at 150 mg/kg/day	2 weeks	Suppression of advanced hyperglycemia Improving fasting insulin-glucose ratio and glucose tolerance Improvement in islet size and number Increased percentage of insulin positive cells and decreased percentage of glucagon positive cells Reduction cell apoptosis in pancreas, liver and kidney Improving insulin signaling in skeletal muscle
42	Nicotineamide + STZ-induced Sprague-Dawley rats	Δ9-Tetrahydrocannabinol (THC) at 3 mg/kg/day	7 days	Reduction inflammation in the kidney Regulation of redox homeostasis in the kidney Preventing the downregulation of KLF-4 in the kidney
43	STZ-induced diabetic C57BL/6J mice	Cannabidiol (CBD) at 10 mg/kg/day	7 days	Hyperglycaemia and glucose intolerance remained unchanged Reduction in T cell infiltration: Increasing glomerular lesions, tubular lesions, fibrotic areas, plasma creatinine and blood urea nitrogen
46	STZ-induced Sprague-Dawley rats	CBD at 10 mg/kg/ every 2 days	2 weeks	Neither body weight nor blood glucose levels changed Preventing diabetes-induced hyperpermeability and nerve cell death in the retina Reduce oxidative and nitrative stress in the retina. Decrease in VEGF and ICAM-1 expression and TNF-alpha level Blocking p38 MAPK activation
51	STZ-induced diabetic C57BL/6J mice Human cardiomyocytes (HCM) cultured in high glucose	CBD at 1, 10, or 20 mg/kg/day	11 weeks 4 weeks	Body weight, blood glucose and pancreatic insulin levels remain unchanged Reduce myocardial dysfunction and cardiac fibrosis Improving myocardial oxidative/nitrative stress, inflammation and cell death Reduces reactive oxygen species, nuclear factor-κB (NF-κB) activation and cell death in HCM
52	STZ-induced Wistar-Kyoto rats	THC at 0.15 mg/kg/day	8 weeks	Improve blood glucose levels and reduce oxidative stress Prevent left ventricular hypertrophy
56	STZ-induced Wistar rats	*C. sativa* extract with an high CBD content at 15 or 30 mg/kg/day	8 days	Ameliorate allodynia and oxidative damage Restore impaired thermal perception and nerve growth factor content
57	29 patients with chronic painful diabetic peripheral neuropathy (DPN)	Sativex [(tetrahydrocannabinol (27 mg/ml) and cannabidiol (25 mg/ml)]	Doses were administered in divided doses up to 4 times a day	No more effective than placebo
58, 60	16 patients with painful DPN	1% THC 4% THC 7% THC	2 weeks	Causes a dose-dependent reduction in DPN pain Pain decreases as plasma THC levels rise
59	100 patients with painful DPN	1-2 drops, 3-4 drops or 5-6 drops of cannabis oil (THC: 3.20 mg/drop, CBD: 0.32 mg/drop, CBN: 0.65 mg/drop)	12 weeks	Decreased multidimensional pain scores Improves painful DPN symptoms.
61	STZ-induced Wistar rats	CBD at doses of 0.1, 0.3, or 3 mg/kg/day	A single dose	Ameliorates allodynia Increase 5-HT level in the spinal cord
62	Human Schwann cells cultured in high glucose STZ-induced Sprague-Dawley rats	CBD (8 μM) and β-caryophyllene+CBD (75 μM + 3.64 μM CBD at doses of 15 mg/kg/ thrice a week	24 hours 3 weeks	Reduction in mitochondrial membrane potential, ROS and mitochondrial superoxides Increased anti-inflammatory effects Prevents the deterioration of the mitochondrial quality control system Reduces pain hypersensitivity, hyperalgesia and allodynia

et al[51] demonstrated that CBD treatment administered to STZ-induced C57/BL6J mice reduced myocardial dysfunction, cardiac fibrosis, oxidative/nitrative stress, inflammation, and cell death. In addition, CBD administration was reported to reduce high glucose-induced increased ROS levels, nuclear factor-κB (NF-κB) activation, and cell death in human cardiomyocytes (HCM). Moreover, chronic low-dose administration of Δ9-THC (a nonspecific CB receptor agonist) to diabetic Wistar-Kyoto rats has been reported to reduce blood glucose levels and improve oxidative stress. It has therefore been suggested that the beneficial changes in biochemical parameters in diabetic rats are due to improvements in myocardial and vascular function caused by Δ9-THC (Table 1).[52]

Cannabis and Diabetic Neuropathy

Diabetic neuropathy (DN), one of the most common complications of diabetes, is characterized by nerve damage resulting from prolonged exposure to high blood glucose levels. The DN develops in more than 50% of people with diabetes.[53,54] In addition to hyperglycemia, oxidative stress, advanced glycation end products, and inflammation are known to play an important role in the development of DN.[55] It has been reported that oral administration of high CBD *C. sativa* extract to diabetic rats improves allodynia, impaired thermal perception, and oxidative damage and may therefore be beneficial in DN.[56] The study to evaluate the efficacy of cannabis in 29 people with painful diabetic peripheral neuropathy (DPN) found that cannabis was no more effective than placebo.[57] On the contrary, a study investigating the efficacy of cannabis in 16 patients with painful DPN reported that inhaled cannabis showed a dose-dependent reduction in DPN pain in patients with treatment-refractory pain.[58] Another randomized clinical trial has provided evidence of the significant therapeutic efficacy of a new transdermal medical cannabis formulation (THC : CBD : CBN) in improving the painful symptoms of DPN. The significant reduction in multidimensional pain scores and favorable safety profile of this formulation provide evidence of significant clinical potential.[59] Wallace et al[60] suggested that plasma THC levels are associated with pain in DPN and that it is important to measure plasma CB levels in studies. It has been suggested that CBD administration to rats with a diabetes-induced neuropathic pain model has both acute and sustained anti-allodynic effects and that this effect is mediated through activation of the serotonergic system via 5-HT1A receptors.[61] According to a recent study, the combined administration of beta-caryophyllene (BC) and CBD to human Schwann cells cultured in high glucose decreased mitochondrial membrane potential, ROS and mitochondrial superoxides. Furthermore, it was reported that the combined treatment of BC and CBD in STZ-induced DN mice increased statistical activity and anti-inflammatory effect, established mitochondrial quality control system and increased pain hyperintensity against hyperalgesia and allodynia (Table 1).[62]

THE STATUS OF CANNABIS IN THE COUNTRY

It is emphasized that cannabis is still widely abused around the world, has addictive potential, and can be an important step in the transition to other drugs. Additionally, various cannabis products and semi-synthetic CBs derived from cannabis have emerged as a result of cannabis policies in some countries. These new products also pose new threats. For this reason, the steps to be taken regarding the cultivation of cannabis for medical use are crucial.[63]

As stated in the legislation, the production, import, export, and sale of cannabis, which is classified as a narcotic substance in the country, is prohibited. To prevent the production of narcotic drugs related to cannabis, authorised institutions have established procedures and principles regarding the determination of cultivation areas, authorization requirements, necessary controls, and procedures to be followed in case of unauthorised cultivation.[64,65]

CONCLUSION

In conclusion, the data reported in this review suggest that the cannabis plant and its CBs, particularly THC and CBD, have therapeutic potential in the management of diabetes and its complications. Studies suggest that these 2 CBs may be important in the treatment of diabetes, particularly due to their antioxidant and anti-inflammatory effects. However, more preclinical and clinical studies are needed to confirm the safety and efficacy of such natural remedies as complementary or alternative treatments for diabetes and its complications.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

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