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Review Article:

Effects of Epigallocatechin-3-Gallate (EGCG) in Diabetes Mellitus as a DYRK1A inhibitor

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Abstract

Background: Diabetes mellitus is a common metabolic disorder characterized by chronic high blood sugar levels due to impaired insulin secretion or action. Existing diabetic medications have limitations, including high costs and the risk of hypoglycemia. **Aim**: To overcome these challenges, researchers are exploring advanced treatments, and one potential path is studying plants and natural sources. Many plants include green tea (*Camellia sinensis*), rich in catechin derivatives, particularly epigallocatechin-3-gallate (EGCG), have shown promising effect because this agent may enhance beta cell proliferation, so it can produce dramatic response in management of diabetes mellitus and it is expected to reduce complication of this disease. Thorough data searching from September 2021 to June 2023 was used to conduct this study. The key terms diabetes mellitus, herbal treatment of diabetes, DYRK1A inhibitor, Epigallocatechin-3-gallate, and beta cell proliferation were concomitantly searched in Google Scholar, Web of Science, and PubMed in order to find relevant material. The publications that are presented here were published between 2014 and 2023. **Conclusion**: Collectively EGCG properties as a DYRK1A inhibitor may enhance β cell proliferation that is promising effects in diabetes mellitus treatment.

1. Introduction

Diabetes mellitus is a prevalent metabolic disorder characterized by chronic hyperglycemia resulting from impaired insulin secretion, insulin action, or both (1). Type I, type II, and gestational diabetes are the three primary types of the disease. Known also as insulin-dependent diabetes, type I diabetes mellitus is characterized by a considerable loss of pancreatic cells. Non-insulin-dependent diabetes mellitus, often known as type II diabetes mellitus (Type II DM), is associated with dysfunctional insulin signaling and/or inadequate insulin production. Obesity, lack of exercise, and genetic susceptibility all have a role in the development of Type II DM. Diabetes-related chronic hyperglycemia can cause a number of secondary illnesses, such as macro and microvascular problems, which, if left untreated, can have serious complications (2, 3).

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Adopting a healthy diet, regulating your weight, and engaging in regular physical activity are the first stages in treating T2DM. Alongside these lifestyle changes, insulin and various medication categories, such as metformin, sulfonylureas, thiazolidinediones, glucagon-like peptide 1 (GLP-1) analogues, glucose-dependent insulinotropic peptide (GIP) and GLP-1 receptor co-agonists, dipeptidyl peptidase-IV (DPP-IV) inhibitors, sodium-glucose co-transporter 2 (SGLT2) inhibitors, and synthetic insulin, are employed as treatments for diabetes (4). Despite being a primary treatment option, insulin has certain limitations, such as its expensive cost, potential for weight gain, risk of hypoglycemia, and inconvenient method of administration (5). Moreover, the synthetic treatments, however, frequently cost a lot of money and are difficult for people in rural and underdeveloped regions to get. They also have a number of undesirable side effects, such as obesity, hepatic and renal diseases, hypoglycemia, and gastrointestinal abnormalities (4).

Recent data indicate that diabetes treatment expenses worldwide are 673$ billion, or nearly 12% of all healthcare expenditures. Finding new medications to control type II diabetes is essential because there is presently no optimum treatment for the disease or its persistent and dangerous

consequences (62). To address these limitations: The escalating incidence of diabetes , its associated complications and its medication drawbacks necessitate the exploration of innovative therapeutic interventions (6, 7) and researchers are dedicating considerable efforts to study plants and other natural sources to discover new treatments for diabetes mellitus (8, 9). Medicinal plants have been used since ancient times in local communities to treat various diseases owing to their numerous health benefits(10). Many of these plants may contain promising therapeutic agents so the studying of active constituents of such plants can open new perspectives for management of diabetes mellitus.

One of these studied plants is Green tea (*Camellia sinensis*) dried leaves which contain a variety of catechin derivatives, The most abundant catechin in green tea is epigallocatechin-3-gallate (EGCG) which is a polyphenolic substance (11). EGCG constitutes about 50% to 80% of all catechins (12). Additionally, it can be derived from a variety of natural sources, including fruits and vegetables (13).

The three aromatic rings (A, B, and D) in flavanol, which builds the chemical structure of EGCG, are connected by a pyran ring (C) (14), as shown in **Figure 1**, EGCG interacts with phospholipids and proteins of the plasma membrane. Additionally, EGCG is carried to intracellular locations such as the nucleus, cytoplasm, mitochondria, and lysosomes, where it mediates numerous biological processes. These diverse outcomes depend on the type of cells, and the EGCG concentrations (15).

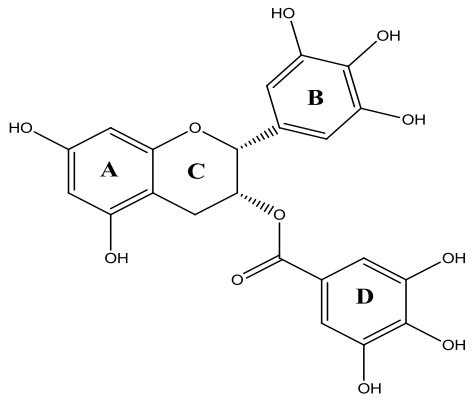

Figure 1. Chemical structure of EGCG (16)

1.1 Diabetes mellitus and herbal treatment

A collection of metabolic conditions known as diabetes mellitus (DM) are characterized by hyperglycemia brought on by inadequate insulin production, insulin action, or both (17). According to the International Diabetes Federation (IDF), in 2021, there were 537 million individuals living with the disease (18). Many investigations have been carried out to determine the function of herbal remedies in the treatment of DM (19). Researchers from all around the world are now paying considerably greater attention to formulations made from medicinal plants (20), since natural medicine can be considered as important source for getting new lead compounds (21). Over 800 plants were identified based on traditional medicinal data as having anti-diabetic effects and having positive impacts on the treatment or prevention of diabetes problems.

The medicinal herbs provide their anti-diabetic effects mainly by restoring the activity of pancreatic β cells that increase insulin secretion or by decreasing dietary glucose absorption (21). These plants include: Acacia nilotica, Adonsonia digitate, Allium cepa, Balanites aegyptiaca, Brassica oleracea, Camellia sinensis and many other plants (22).

Camellia sinensis (Green tea) phenolic constituents have antidiabetic effects by inhibiting α-glucosidase, preventing oxidative stress (23), Moreover, they work by altering the activity of dipeptidyl peptidase (24). The majority of the plant's catechins is EGCG, and it may be the cause of some of green tea's effects (25).

EGCG has effects on type I and type II DM. In type I DM by limiting reactive oxygen species (ROS) and inflammatory factors in vitro or by suppressing the production of inducible nitric oxide synthase (an enzyme that produces nitric oxide) (26), EGCG may protect the function of pancreatic β cells. Moreover, in the case of mice with iron-loaded pancreas, green tea was also able to encourage β cells to release more insulin by about 2 folds (27). In type II DM, EGCG improves insulin sensitivity (28) by phosphorylating the insulin receptor substrate-1 (IRS-1) as a result of EGCG causing the 5′-adenylic acid-activated protein kinase pathway to override the insulin stress signaling pathway closure (29).

By increasing the number of insulin-signaling proteins in insulin-resistant rats, it may be possible to outperform the sensitivity of insulin. By inhibiting ROS, which can block insulin signal transduction and prevent IRS-1 from binding to the insulin receptor by lowering c-jun NH2-terminal kinase (JNK) phosphorylation, EGCG can reduce insulin resistance (30).

EGCG at a concentration of 6 mg/liter of water is effective in considerably lowering fasting blood sugar, according to research on streptozotocin-induced hyperglycemic zebrafish (31). According to research on tissue, EGCG decreases the synthesis of glucose via suppressing hepatic gluconeogenesis by downregulating the expression hepatocyte nuclear factor's gene and activating activated protein kinase. Moreover, EGCG can reduce the synthesis of glucose by boosting the insulin receptor and controlling the genes that code for gluconeogenic enzymes (32).

These findings demonstrated that EGCG action resemble insulin action by upregulating the tyrosine phosphorylation of the insulin receptor, insulin receptor substrate-1, phosphoinositide 3-kinase, and mitogen-activated protein kinase activity and downregulating the expression of the gene encoding the phosphoenolpyruvate carboxykinase (33). Also, it was shown that EGCG decreased plasma glucose levels in diabetes via inhibiting of salivary α- amylase (34) preventing α-glucosidase activity that inhibit starch's hydrolysis (35-37). Additionally, EGCG has the ability to reduce the inhibition of the insulin signaling pathway brought on by TNF-α (38).

During the cell culture study, it was observed that EGCG effectively stimulates the secretion of Glucagon-like peptide 1 (GLP-1) with a significant p-value of 0.0001(39). Moreover, catechin might aid in adipocyte differentiation and improve insulin sensitivity by strongly activating the PPAR-γ (30). EGCG can help with obesity, which is a contributor factor to type II diabetes through a modulation involving different organs such as adipose tissue or the liver and also noted that EGCG consumption inhibits pancreatic lipase in vitro

and suppresses postprandial serum triglycerides in a dose-dependent manner (40, 41). Additionally, EGCG's ability to interfere with the enzymes glucosidase and amylase may help in weight reduction (42).

1.2 Role of EGCG as a DYRK1A blocker in beta cell proliferation

Beta cell proliferation: Insulin levels in the blood are determined by the mass of beta cells (β cells) and the activity of insulin secretion. The determinant of β cell mass is beta cell proliferation. The mechanism that controls the number of β cells in the body has yet to be discovered (43). In recent years, there has been significant interest in a new strategy in diabetes treatment that involves increasing β cells multiplication while decreasing β cells death (44). When it comes to type II diabetes, β cell mass dramatically decreases during the course of the disease, falling by more than 54% in people with more than 15 years of diabetes (45). In recent years, scientists discovered that DYRK1A inhibitors have an effect on β cells replication, indicating that their efforts to promote β cells replication were successful (46).

The calcineurin-NFAT-DYRK1A pathway is involved in β cell proliferation. When intracellular calcium (Ca^{2+}) level is risen due to glucose or medicines (sulfonylureas) or any other stimulator that result in activation of Calmodulin (CAM), causes the calcineurins A (Cn A) and B (Cn B) to be activated (CnB). The dephosphorylation of the the nuclear factor of activated T cells (NFAT) family transcription factors by these phosphatases (CnA and CnB) results in NFAT translocation to the nucleus. In this case, NFAT activates the promoters of cyclins E and A, as well as cyclin-dependent kinase 1 (CDK1), while inhibiting the promoters of cell cycle inhibitor genes CDKN2A, CDKN2B, and CDKN1C, resulting in cell cycle entrance and proliferation (47, 48).

DYRK1A: It is a protein kinase enzyme that belongs to the dual-specificity tyrosine phosphorylation-regulated kinase 1 A (DYRK1A) family. Five isoforms in this family, divided into two groups, DYRK1A belongs to class I (49). It is involved in the etiology of Down syndrome and has important biological activities. In addition, DYRK1A mutations in mammals cause problems in neuroblast proliferation and aberrant brain growth development (43). DYRK1A causes the buildup of amyloid beta (A) peptides, which leads to Tau hyperphosphorylation and neurodegeneration. In addition, changes in DYRK1A expression have been linked to cancer and diabetes (50). The function of DYRK1A in the β cells' proliferation, as illustrated in **Figure 2,** is to rephosphorylate NFAT factors, export them back to the cytoplasm, and stop the proliferation of β cells (51). The fact that DYRK1A inhibitors allow β cell growth is of pharmaceutical importance (52). The studies of DYRK1A inhibitors activity have increased dramatically in recent years (50).

DYRK1A inhibitor: According to Dirice E. study, a 5-iodotubercidin, " a DYRK1A inhibitor" was able to causes a substantial and specific increase in human beta-cell proliferation both in vitro and in vivo (53).Wang. P. found that regeneration of beta cell mass was substantially more rapid in the harmine-treated mice than in the controls, reaching near-normal values in only fourteen days. In vitro and in vivo, Harmine and INDY stimulated human beta cells to enter the cell cycle, with beta cell labeling indices that are similar to those seen in people during the first year of life (54). Harmine, Torin and other DYRK1A inhibitors found to promote the activity and proliferation of β cell during study of their effects on cell culture (55). Harmine increased β cell mass and regeneration in a mice model and improved glycemic control and β cell proliferation in vivo in two additional typical human islet transplant models, one euglycemic and one diabetic (54).

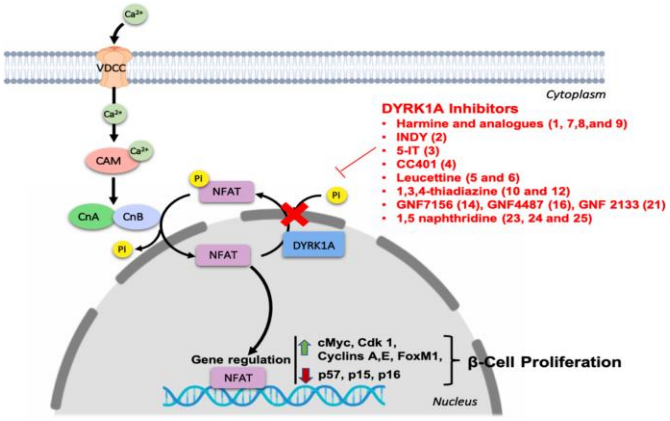

Figure 2. Mechanism of DYRK1A-NFAT mediated human β-cell proliferation: Ca+2, calcium. VDCC, voltage-dependent calcium channel. CAM, calmdulin. NAFT, Nuclear factor of activated T-cells. CnA and CnB, calcineurins **(47)**

EGCG as DYRK1A inhibitor: EGCG is known to inhibit DYRK1A (IC_{50} 0.33μM) (56). DYRK1A is a key factor in the phenotypic of Down syndrome. Mice overexpressing DYRK1A in certain chromosomal

mutations condition has shown cognitive deficits, which has been thought to be improved by EGCG through inhibition of DYRK1A (57, 58). In an animal study conducted on Down syndrome mice, the relationship between EGCG and DYRK1A was investigated. The mice were administered EGCG for a period of one month, and the effectiveness of EGCG on DYRK1A was assessed by measuring the biomarker homocysteine, there is a correlation between the plasma level of homocysteine and DYRK1A expression. The study revealed a significant effects on homocysteine level and DYRK1A expression ($p<0.01$), indicating notable effects of EGCG on DYRK1A activity (59).

Studies on the effects of EGCG on diabetes mellitus include one by Wenru Li (2020), which discovered that a high dose of EGCG influenced glycated hemoglobin (HbA1c) and fasting blood sugar that is equal to or higher than that of metformin. With metformin or EGCG administration, the number and density of β cells increased, indicating that EGCG and metformin therapies had similar effects (60). Zhu T, conducted a study on diabetic rats with different doses of EGCG for ten weeks and compared their effects to that of metformin. They found significant effects of 50 and 100 mg/kg/day on fasting, postprandial blood glucose, fasting serum insulin (FSI) and homeostasis model assessment of insulin resistance (HOMA-IR) (61).

Even though there are numerous instances of EGCG's impacts as a DYRK1A inhibitor, it has a number of issues with oral uptake, such as low permeability, chemical instability, and metabolic biotransformation (62, 63).

1.3 EGCG pharmacokinetic properties and improving strategies

EGCG is unstable in both neutral and alkaline conditions, rapidly degrades via the protonation of hydroxyl groups, then undergoes several biotransformation processes before losing its biological activity. As a result, EGCG is poorly stable and has a low bioavailability (64). The limited bioavailability of EGCG is also related to several reasons, such as EGCG conversion to different methylated, glucuronidated, and sulfate metabolites and active removal of numerous polyphenolic compounds by the multidrug resistance-associated protein 2 (MRP2). According to studies, plasma EGCG concentrations can be as high as 2% of the amount consumed. Therefore, it is necessary to create a plan that can boost EGCG's bioavailability and stability (65).

The chemical stability issues of EGCG are associated with epimerization and oxidation that is related to temperature and pH. The most effective method to prevent EGCG from degrading is to synthesize chemical derivatives that cover some or all of the hydroxyl groups in EGCG with acyl groups through ester bonds (66). While molecular alteration, co-administration with certain additional bioactive substances, and the use of nanostructure-based drug delivery methods can all help to enhance EGCG's poor permeability (67).

2. Conclusion

In conclusion, EGCG has been shown to effectively inhibit DYRK1A and can enhance β cell mass. Additionally, in diabetes-related research, EGCG exhibits promising effects on glycated hemoglobin and fasting blood sugar levels comparable to metformin, suggesting potential therapeutic value. However, despite its beneficial properties as a DYRK1A inhibitor, EGCG faces challenges with oral uptake due to issues such as low permeability, chemical instability, and metabolic biotransformation. Addressing these concerns could enhance its clinical utility and efficacy as a potential treatment option for diabetes mellitus.

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الأمكانيات العلاجية لـ Epigallocatechin-3-gallate (EGCG) كمثبط لـDYRK1A في مرض السكري: نظرة عامة

الخلاصة

المقدمة: مرض السكري هو اضطراب أيضي شائع يتميز بالارتفاع المزمن لمستويات السكر في الدم نتيجة لانخفاض إفراز الأنسولين أو عدم فعاليته. تتضمن الأدوية الموجودة للمصابين بالسكري بعض القيود، مثل التكلفة العالية وحدوث نقص في مستوى السكر في الدم. **الهدف:** للتغلب على هذه التحديات، يقوم الباحثون بدراسة العلاجات المتقدمة، ومن بين السبل المستخدمة هي دراسة النباتات والمصادر الطبيعية. أظهرت العديد من النباتات ومن بينها الشاي الأخضر، الغنية بمشتقات الكاتيشين، بما في ذلك إبيجالوكاتيشين-3-غالات (EGCG) فوائد علاجية محتملة في علاج مرض السكري عن طريق تحفيز خلايا بيتا المسؤولة عن انتاج الانسولين وقد يكون لها تاثير في تقليل مضاعفات هذا المرض. وقد تم استخدام البحث الشامل عن البيانات من ايلول 2021 إلى حزيران 2023 لإجراء هذه الدراسة. تم البحث عن المصطلحات الرئيسية "داء السكري ، والعلاج بالأعشاب لمرض السكري ، ومثبط DYRK1A ، و "Epigallocatechin-3-gallate"و "تكاثر خلايا بيتا" في Google Scholar و Web of Science و PubMed. تم هنا عرض المنشورات المقدمة بين عامي 2014 و 2023. **الاستنتاج:** بشكل عام، تَعزز خصائص EGCG كمثبط DYRK1A تكاثر خلايا البيتا وهذه من التاثيرات الواعدة في علاج مرض السكري.

الكلمات المفتاحية: الكاتيشين، DYRK1A، مرض السكري، خلايا البيتا