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Caffeic Acid - A Potent Phytocompound against Diabetes Mellitus A Review

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Abstract

Diabetes mellitus, a metabolic syndrome characterized by chronic hyperglycemia causes serious morbidity and mortality worldwide. Several allopathic drugs are available to treat diabetes but management without any side effects is still a challenge to the medical system; hence phytocompounds are getting more importance. Number of plant based compounds has been identified as potential antidiabetics. Caffeic acid, isolated from edible plant species has wide range of pharmacological effects. Recently, antidiabetic activities of caffeic acid are being explored. This review of the current literature discuss in detail about the antidiabetic actions of caffeic acid, including; antidegenerative effect on islets, up-regulation adipocytes GLUT-4,

inhibition of alpha-amylase and alpha-glucosidase activity, increase mRNA expression of glucokokinase, decrease in glucose-6-phosphatase and phosphoenolpyruvate carboxykinase activities and regulation of beta-cell function.

Keywords: Antidiabetic activities, Caffeic acid, Diabetes mellitus.

Introduction

Diabetes mellitus is a heterogeneous group of disorder with life threatening complications. It is defined as a metabolic syndrome characterized by chronic hyperglycemia with disturbance in carbohydrate, fat and protein metabolism [1]. It results from lack of insulin secretion from pancreatic B-cells "Insulin Dependent Diabetes Mellitus" or decrease in sensitivity of tissue to metabolic effect of insulin "Non insulin Dependent Diabetes Mellitus" [2] .

World Health Organization has projected diabetes as a major public health concern worldwide both in the developed and developing countries. India is one of the leading countries for number of people with diabetes mellitus[3]. In the face of global epidemic, management of diabetes with safer and cost effective medication is still a challenge to medical system[4]. Hence, research on potential biomolecules as a source of alternative medicines is getting more importance.

Large number of flowering plants having antidiabetic properties have been discussed in literature but the exploration of potential compounds and pharmacological and molecular mechanisms are often limited. Although, number of antidiabetic phytocompound has been isolated, caffeic acid is gaining more attention as it exhibit potent antidiabetic activity through number of mechanisms. It is present in edible plants and is non toxic[5]. The antihyperglycemic effect of caffeic acid isolated from the fruit of *Xanthium Strumarium* was fist reported by Hsu et al.[6]. In the study, marked plasma glucose lowering effect in dose dependent manner was observed in streptozotocin-induced diabetic rats and rats with insulin-resistance. Since then, dntidiabetic mechanisms of caffeic acid have widely been studied and reported in number of literature. Hence, the main aim of this review is to provide the available data about the wide range of pharmacological actions of caffeic acid against diabetes mellitus.

Chemical identification and structure

Caffeic acid ($C_9H_8O_4$. Molecular Weight = 180.16) is also called:

3-(3,4-Dihyroxyphenyl)-2-propenoic acid,

5(4)-(2-Carboxyethenyl)-1,2-dihydroxybenzene,

4-(2' -Carboxyvinyl)-1,2-dihydroxybenzene,

3,4-Dihydroxybenzeneacrylic acid,

3,4-Dihydroxycinnamic acid,

3-(3,4-Dihydroxyphenyl)propenoic acid

and 3-(3,4-Dihydroxyphenyl)-2-propenoic acid[7].

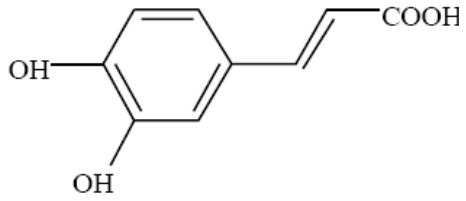

Figure 1: Structure of caffeic acid[7].

Chemical and physical properties

Caffeic acid is naturally occuring hydroxycinnamic acids, the most widely dispersed class of phenylpropanoids in plants[8]. It appears as Yellow prisms or plates from water[9]. It is sparingly soluble in cold water; very soluble in hot water and cold ethanol[10]. Caffeic acid exists in cis and trans forms, trans being the predominant naturally occurring form[11]. Solutions of caffeic acid and its derivatives (chlorogenic and isochlorogenic acids) are unstable in sunlight and ultraviolet light[12].When solutions of caffeic acid is exposed to sunlight or ultraviolet light, the *trans* form of caffeic acid is partially converted to the *cis* form, which may be converted to the lactone and aesculetin[13].

Occurrence

Caffeic acid has been isolated from numerous dicotyledenous plant species belonging to the Families *Caprifoliaceae*, *Compositae*, *Cruciferae*, *Cucurbitaceae*, *Labiatae*, *Leguminosae*,

Polygonaceae, *Saxifragaceae*, *Solanaceae*, *Theaceae*, *Umbelliferae*, and *Valerianaceae*[14] . It exist in many fruits, vegetables, several grains, and beverages including blueberry, kiwi, cherry, plum, apple, pear, chicory, artichoke, potato and cider[15]. Coffee is a good source of caffeic acid, particularly in its esterified form, chlorogenic acid (5-caffeoylquinic acid)[16].

Pharmacological properties

Caffeic acid has been reported to have wide range of pharmacological properties[17,18]. Apart from its actions like; inhibition on cancer cell proliferation[19], powerful antioxidant[20,21], immunomodulatory[22], antimicrobial[23], anti-agining[24] and anti-inflammatory activity[25,26,27], currently, caffeic acid has been widely investigated to have antidiabetic activity.

Antidiabetic action

Caffeic acid acts via number of mechanism against hyperglycemia[6]. It regulates beta cell function as well as exerts antidegenerative effect on islets, up-regulates adipocytes GLUT-4, inhibits alpha-amylase and alpha-glucosidase activity in the gastrointestinal tract and increases glucokinase activity in the hepatocytes. Caffeic acid has also been reported to reduce glycosylated hemoglobin level exerting long term diabetic control. It also increases plasma insulin, C-peptide, and leptin levels. Caffeic acid lowers glucose-6-phosphatase and phosphoenolpyruvate carboxykinase activities and their respective mRNA expressions. These mechanisms have been reported in several literature which are discussed below.

Regulates β-Cell Function

The ability of beta cells in the pancreatic islets to secrete adequate amounts of insulin depends on its function and mass[28]. Several trials have identified the continuing loss of effective beta-cell function, a key determinant of deteriorating glycaemic control and progressive failure of all types of therapy[29]. Chronic hyperglycaemia leading to impaired insulin secretion and beta-cell turnover has been well established[30]. Caffeic acid has been reported to have its actions on pancreatic beta-cell function. It exerts anti-degenerative effects and promotes the survival of islets in animal model. In the study conducted by Jung et al.[31], in mice, caffeic acid has been found to preserve islet normal histological appearance against the control which exhibited islet boundary definition

loss and degeneration.

Increases glucokinase activity

Glucokinase facilitates phosphorylation of glucose to glucose-6-phosphate, decreasing the hepatic output of glucose[32]. It is considered a strong candidate target for antihyperglycemic drugs for type 2 diabetes as mutations in the glucokinase gene causes serious impact on glucose homeostasis[33]. Caffeic acid suppresses the hepatic glucose output by enhancing hepatic glucose utilization and inhibiting over glucose production[34] . It has been reported that there has been marked enhancement in glucokinase mRNA expression as well as increase in genes expression of glucose-6-phosphatase, a key enzyme that control gluconeogenesis in animal treated with caffeic acid[31,35].

Up-regulates adipocyte GLUT4

Insulin resistance is the earliest defect in developing type 2 diabetes. It involves decreased glucose transport and metabolism in muscle and adipocytes. The adoipose GLUT4, a membrane bound glucose transporter mediates insulin-stimulated glucose uptake in adipocytes. In type 2 diabetes, GLUT4 expression is decreased in adipose tissue[36,37]. Caffeic acid enhance the GLUT4 protein expression in adipose tissue[31,34].

Inhibits key enzyme

Pancreatic alpha-amylase is a key enzyme in the digestive system and catalyses the initial step in hydrolysis of starch to a mixture of smaller oligosaccharides. These are then acted upon by alpha- glucosidases and further degraded to glucose that on absorption enters the blood stream which elevates postprandial hyperglycemia. Inhibitors of pancreatic alpha-amylase delay carbohydrate digestion, lowering the postprandial serum glucose levels. These enzyme inhibitors are widely studied and isolated from plants[38]. Caffeic acid is reported to inhibit the α-amylase and α-glucosidase activities in a dose-dependent manner in vitro[39].

Conclusions

Diabetes mellitus, a disease known to man for many millennia, continues to rise world wide. There has been significant progress in the development of drugs to cure diabetic complications but the numerous side effects are still a serous concern. Hence, there is increasing demand by the

diabetic population to use safer and cost effective natural products. Medicinal herbs have a long history of use in alternative and complementary medicine systems. Currently, number of plant derived antidiabetic molecules has been isolated. Understanding of the mechanisms through which these biomolecules mediate diabetes mellitus is evolving. They are generally being viewed as molecule modulating multiple metabolic pathways.

Caffeic acid is evolving as potential therapeutic agent based on its multiple targeting actions against diabetes. In this review, we summarize the various mechanisms by which caffiec acid prevents and treats diabetic complications. Systematic information about this potent biomlecule and its mode of antidiabetic actions will pave the way for further research. Additionally, therapies based on such active biomolecule constitute a novel pharmacological approach for the treatment of diabetes mellitus.

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