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REVIEW ARTICLE

Secoisolariciresinol Diglucoside (SDG) from Flaxseed in the Prevention and Treatment of Diabetes Mellitus

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Abstract

This review focuses on the role of reactive oxygen species (ROS) on the development of type 1 and type 2 diabetes and its treatment with secoisolariciresinol diglucoside (SDG) isolated from flaxseed which is an antioxidant and suppresses phosphoenolpyruvate carboxykinase (PEPCK) gene expression, a rate- limiting enzyme in the gluconeogenesis in the liver. Role of ROS in the development of type 1 diabetes [diabetic prone Bio Breeding (BBdp) rats and streptozotocin-induced diabetic (STZ) rats and type 2 diabetes (Zucker diabetic fatty female rats, ZDF rats)] has been discussed. Oxidative stress has been assessed by measuring serum and pancreatic malondialdehyde (MDA), pancreatic chemiluminescence (pancreatic-CL) and oxygen radical producing activity of white blood cells (WBC-CL). Diagnosis of diabetes was made by hyperglycaemia and glucosuria. Incidence of diabetes was 100 % in SDZ rats, 72 % in BBdp rats and 100 % in ZDF rats by the age of 72 days. Development of diabetes was associated with increases in the serum and pancreatic MDA, WBC-CL and pancreatic-CL and glycated haemoglobin (HbA_1c). SDG prevented the development of diabetes by 75 % in STZ rats, by 71 % in BBdp rats and by 20 % at 72 days of age in ZDF rats. However, 80 % of the rats which did not develop diabetes by 72 days of age, developed diabetes later on, suggesting that SDG treatment delays the development of diabetes in ZDF rats. Treatment with SDG decreased the levels of serum and pancreatic MDA, WBC-CL and pancreatic-CL. In conclusion, development of type 1 and type 2 diabetes is mediated through oxidative stress and the prevention or delay in the development of diabetes with SDG could be due to its antioxidant activity and its suppressant effect on PEPCK enzyme. Lignan complex which contains 34 % to 38 % of SDG is effective in lowering serum glucose and HbA_1c in type 2 diabetes in humans.

Key words: Type 1 diabetes; Type 2 diabetes; Oxidative stress; Antioxidants; Phosphoenolpyruvate carboxykinase (PEPCK); Malondialdehyde; Pancreatic -CL; WBC-CL; Secoisolariciresinol diglucoside (SDG).

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Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder characterised by persistent hyperglycaemia caused by impaired insulin secretion and resistant to peripheral insulin action or both. There are three types of DM: type 1 DM, type 2 DM and gestational DM. Type 1 DM is characterised by autoimmune destruction of β-cells in pancreas and accounts for 5 % to 10 % of DM. Type 1 DM is commonly observed in children and adolescents. It may occur in people with any age. Type 2 DM accounts for approximately 90 % of DM. In this type of DM there is a reduction in response to insulin. Ineffec-

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tiveness of insulin in the initial stage is countered by an increase in production of insulin, but later on there is a loss of production of insulin resulting in type 2 DM. Type 2 DM is mostly observed in people older than 45 years of age. Gestational DM occurs during pregnancy. The incidence of type 1 DM is 15 per 100,000 people and prevalence is 9.5 per 10,000 in the world.[1] The incidence and prevalence respectively are 20 per 100,000 and 12.2 per 10,000 people in USA, 15 per 100,000 and 12.2 per 10,000 people in Europe and 15 per 100,000 and 6.9 per 10,000 people in Asia.[1] The prevalence of type 2 DM globally is 6059/100,000 people and projected to be 7079/100,000 people by 2030.[2] There is equal distribution of type 2 DM in male and female and the incidence peaks at about at 55 years of age.[2] Presently, the treatment of DM includes insulin, insulin secretagogues and insulin sensitising drugs, thiazolidinedione for glycaemic control. Direct and indirect cost of treatment of type 2 DM is very high.[3, 4] The discovery of cheap plant food or its constitutes would be helpful in the prevention and treatment of DM.

This review paper deals with the role of oxidative stress, defined as a shift in balance between reactive oxygen species (ROS) and antioxidants in favour of ROS in the development of DM and use of secoisolariciresinol diglucoside (SDG) isolated from flaxseed in the prevention and treatment of type 1 DM and type 2 DM. Flaxseed and its components and the mechanism of action of SDG is also described in detail.

Flaxseed and Its Components

Flaxseed contains 38 % to 45 % of its mass as oils of which 51 % to 55 % is α-linolenic acid.[5, 6] The rest of flaxseed is called flax meal which contains approximately 16.4 mg/g of SDG.[7] Most of the SDG is present in the seed coat.[8] The amount of SDG in 100 g of flaxseed is about 0.6 g to 6.0 g.[9] Flaxseed is the richest source of plant SDG.[10] The other components isolated from flaxseed are flax lignan complex which contains 34 % to 38 % of SDG, 15 % to 21 % of cinnamic acid glucoside and 9.6 % to 11.0 % of hydroxymethylglutaric acid.[11] Protein content of flaxseed by weight is about 10.5 % to 31.0 % while the fibre content is about 25 % to 28 % of which 25 % is in soluble form.[12]

Reasons SDG Could be Effective in Prevention and Treatment of Diabetes Mellitus

There are two reasons for which SDG could be effective in prevention and treatment of DM: antioxidant activity and hypoglycaemic effect due to suppression of phosphoenolpyruvate carboxykinase (PEPCK) gene expression.

1. Antioxidant activity

ROS have been implicated in the development of DM and its complication.[13, 14] Dimethylthiourea, a free radical scavenger protected the β-cells of pancreas.[15] ROS may be involved in type 2 DM because plasma levels of free radicals are positively correlated with fasting plasma insulin[16] and malondialdehyde (MDA), an indirect measure of ROS, is also elevated in type 2 DM.[17] ROS have been suggested to be a pathogenic mechanism of insulin resistance and DM.[18] Considering the above reports, antioxidants may be of value in the treatment of DM. The question arises, if SDG has antioxidant activity. Using high pressure liquid chromatography (HPLC), it has been shown that SDG scavenges hydroxyl radical (·OH) generated by photolysis of hydrogen peroxide (H_2O_2) with ultraviolet light and trapped with salicylic acid and this effect was concentration dependent.[19] This investigator also reported that SDG prevented the ·OH-induced lipid peroxidation of liver homogenate in concentration dependent manner by measuring malondealdehide.[19] The antioxidant activity of SDG and its metabolites was investigated using chemiluminescence (CL) of zymosan-activated polymorphonuclear leukocytes (PMNLs) [PMNL-CL]. Activated PMNLs generate numerous oxygen radicals [superoxide anion, H_2O_2, ·OH, singlet ($^1O_2$)].[20-22] There was a concentration-dependent reduction in PMNL-CL with SDG suggesting that SDG has antioxidant activity which was 1.27 times greater than vitamin E. The above data suggest that SDG has antioxidant activity.

2. Hypoglycaemic effect of SDG by suppressing PEPCK gene expression

Increased glucose level in DM is due to increased hepatic neoglucogenesis[23, 24] PEPCK is a rate limiting enzyme for gluconeogenesis in liver[25] and is elevated in all types of DM.[26-29] Regulation of

activity of PEPCK is controlled through gene expression.[30] SDG has been reported to suppress the PEPCK gene expression.[31] SDG could be a good antidiabetic agent. Troglitazone, a known antidiabetic agent suppresses PEPCK gene expression[32] and is an antioxidant.[33]

Reactive Oxygen Species (ROS) and Diabetes Mellitus

As mentioned earlier, ROS may be involved in the development and complication of DM.[13, 14] The common pathway of cell destruction may be due to production of cytokines such as interleukin-1 (IL-1), tumour necrosis factor-α (TNF-α) from activated macrophages. IL-1 and TNF-α activate macrophages[34] and polymorphonuclear leukocytes (PMNLs)[35, 36] to generate ROS which would have lethal effect on islet cells. Cytotoxicity of ROS is due to peroxidation of unsaturated fatty acids in the membrane resulting in lipid peroxidation product MDA that produces a change in cell permeability, integrity and ultimate cell death.[37, 38] Pancreatic cell death would reduce insulin levels resulting in increased serum levels of glucose.[39] It has been reported that cytokines increase the MDA content of islet cells and islet cells necrosis and lazaroid U78518E, an inhibitor of lipid peroxidation, significantly decreased the cytokine-induced increase in islet MDA and protected islet β-cells from destruction by the cytokines.[40] Considering the above data, SDG an antioxidant would prevent and/or delay the development of DM.

A. Effects of SDG on animal model of type 1 and type 2 diabetes mellitus

Beneficial effects of SDG in experimental type 1 and type 2 diabetic animals have been reported by Prasad et al.[41-43]

1. Effects of SDG in animal model of type 1 diabetes mellitus

Two models of type 1 DM have been used for this study: diabetic prone bio breeding diabetic prone rats (BBdp rats) and streptozotocin (STZ)-induced DM. Effects of SDG on these two models of type 1 DM are discussed below.

a) Effects of SDG in BBdp rats

Genetic BBdp rats develop DM spontaneously[44] and is a model of human type 1 DM (insulin-dependent DM). The incidence DM in in BBdp rats is 40 % to 70 %, more than 85 % develop DM by the age they reach 60-120 days. The objectives of the investigator for this study were to determine if SDG prevents or reduces the development of DM and if prevention /reduction in the development of DM is associated with reduction in serum glucose, serum and pancreatic MDA and antioxidant reserve of the pancreas.[42] SDG prevented the development of DM by about 71 %. Serum glucose levels were higher in BBdp rats that developed DM than those that did not develop DM. Serum glucose levels were lower in SDG treated rat that did not develop DM. Serum and pancreatic levels of MDA were elevated in BBdp rats that developed DM. Pancreatic -CL activity (antioxidant reserve) levels in untreated BBdp rats were higher than that of control group suggesting that antioxidant reserve was lower in the diabetic rats. The pancreatic -CL activity in SDG treated BBdp rats was significantly lower than that of untreated BBdp rats suggesting that antioxidant reserve was higher in SDG treated rats than untreated BBdp rats. The above data suggest that type 1 DM in BBdp rats is associated with increases in serum and pancreatic MDA and a decrease in the antioxidant reserve. Oxidative stress (levels of ROS) levels were higher in diabetic rats. These data also suggest that type 1 DM is associated with an increase in the lipid peroxidation product and a decrease in antioxidant reserve. Prevention in development of DM with SDG was associated with a reduction in serum and pancreatic MDA and an increase in the antioxidant reserve. In summary, DM in BBdp rats is mediated through ROS and that SDG prevents the development of DM through its antioxidant activity.[19] Decreased incidence of development of DM in BBdp rats with SDG could also be due to its inhibitory effect on PEPCK gene expression.[31]

b) Effects of SDG on streptozotocin-induced diabetes mellitus in rats

The purpose of this study was to investigate if streptozotocin (STZ)-induced DM is associated with increased oxidative stress (imbalance between oxidants and antioxidants in favour of oxidants)[45] and if SDG reduces/prevents the development of DM by reducing the levels of ROS.[41] Prasad et al[41] investigated the effects of SDG on streptozotocin-induced changes in serum glucose, urinary glucose, serum and pancreatic MDA, ROS producing activity of white blood cells (WBCs) chemiluminescence [WBC-CL)

and antioxidant reserve of pancreas (pancreatic -CL) in Sprague Dawley rats. They reported that STZ-induced DM (increased serum levels of glucose) was associated with an increased levels of glucose in serum and urine, MDA in serum and pancreas, pancreatic antioxidant reserve (pancreatic-CL) and WBC-CL streptozotocin produced in 100 % of rats. SDG treatment prevented the development of DM by 75 % and this was associated with decrease in the levels of glucose in urine and serum, serum and pancreatic MDA and WBC-CL and increase in pancreatic antioxidant reserve. The above data suggest STZ-induced DM is mediated through ROS and prevention of DM by SDG is because of its antioxidant property.[19] The prevention of DM with SDG could also be due to suppression of PEPCK gene expression.[31]

2. Effects of SDG on animal model of type 2 diabetes mellitus

An extensive study on the effects of SDG in the prevention of development of type 2 DM in experimental animal have been carried out by Prasad.[43] The main objectives of this study were if type 2 DM is associated with increases in oxidative stress, if SDG can prevent/reduce the development of type 2 DM and if prevention/reduction in the development of type 2 DM is associated with reduction in oxidative stress. The study was conducted on Zucker diabetic fatty (ZDF) /Gmi-fa/fa female rats, a model of human type 2 DM. DM was assessed by measuring glucose in the urine. Glucosuria started developing at the age of 64 days and all rats developed glucosuria by 72 days of age. Incidence of DM in untreated rats was 100 %. Only 20 % of the SDG-treated rats developed DM by 72 days of age suggesting that SDG treatment delayed the development of DM in 80 % of the SDG-treated rats. Blood glucose levels at the age between 72 and 101 days increased significantly compared to the levels at the age of 42 days in untreated and SDG treated ZDF rats that did develop DM, but the levels of blood glucose in SDG-treated rats (80 %) that did not develop DM, did not increase. Glycated haemoglobin (HbA_1c) was elevated in untreated but not in SDG-treated ZDF rats. Serum MDA levels were elevated in untreated and SDG-treated rats with DM but were lower in SDG-treated ZDF rats at the age 70 days that did not developed DM. The delaying of development of DM with SDG is due to its antioxidant activity. The protective effect of SDG could also be due to its suppressive effect on PEPCK gene expression.[31] There are no reports on the effects of SDG on DM in human.

The data suggest that type 2 DM is associated with increased oxidative stress and SDG delays the development of type 2 DM which is associated with decrease in oxidative stress. Also SDG delay the development of type 2 DM.

B. Flax lignan complex (FLC) on human type 2 diabetes mellitus

As mentioned above, effects of SDG in human in type 1 diabetic patients are not available in literature. However, the effects of flax lignan complex (FLC) on type 2 DM have been reported in literature. Pan et al[46] have reported that FLC in a randomised, double-blinded cross-over trial in type 2 diabetic patients, FLC reduced HbA_1c, fasting glucose, HbA_1c and insulin levels during the lignan treatment phase. The reduction in HbA_1c levels in serum was significant. It is to note that SDG content in FLC is only 34 %. It is possible that the poor effect of FLC on glucose and insulin was because of lower dose (360 mg daily) of FLC. In other double-blinded, randomised, cross-over study, Barre et al[47] have shown that FLC in the dose of 600 mg daily reduced the plasma glucose and HbA_1c significantly. In summary, flax lignan complex seems to reduce the serum/plasma levels of glucose and HbA_1c in patients with type 2 DM.

Perspectives

The above data indicate that ROS are involved in development of type 1 and type 2 DM[41-43] and that SDG isolated from flaxseed prevents the development of type 1 DM[41, 42] and delays the development of type 2 DM[43] in experimental model of DM.

Increases in the serum levels of glucose could be due to decreases in the levels of insulin. It has been reported that insulin induces suppression of gluconeogenesis by inhibiting PEPCK enzyme.[48] ROS cause pancreatic β-cell dysfunction leading to reduction in insulin in the blood.[49] Increased levels of ROS negatively affect β-cell function including insulin secretion.[50] Increase in the serum levels of glucose could also be due to increased expression of PEPCK gene.[51, 52] PEPCK is a rate limiting enzyme for gluconeogenesis in liver[25] and is elevated in all types of DM.[26-29] Decreases in serum levels of glucose with SDG could be due to its anti-oxidant activity[9, 19, 20] and its inhibitory effect on PEPCK enzyme.[31]

MDA is an indirect measure of levels of ROS. Increased levels of MDA could be due to increased production or reduced destruction of ROS. Glucose increases the production of ROS through autooxidation and nonenzymatic glycation of protein.[53.] Several lipid soluble vitamins (Vitamin E, Vitamin A), glutathione peroxidase and glutathione are antioxidants and protects the ROS-induced tissue damage.[41] Increased levels of MDA in serum and pancreatic tissue in experimental DM could be due to increased levels of ROS.[54] Low levels of serum and pancreatic MDA with SDG treatment could be due to reduction in levels of ROS.

Pancreatic-CL measures the levels of antioxidants, glutathione peroxidase and glutathione.[47] The levels of WBC-CL which measures the generation of ROS from WBCs are elevated in streptozotocin induced DM and BBdp rats.[41, 42] The levels of WBC-CL were reduced with SDG in the streptozotocin and BBdp rats.[41, 42] Serum glucose levels were elevated in both type 1 and type 2 DM and SDG treatment reduced the serum levels of glucose.[41-43] Increases in the levels of serum glucose in DM could be due to reduction in the insulin levels because of destruction of pancreas with ROS.

The available data suggest that type 1 DM is associated with increased generation of ROS by WBCs, decrease in the antioxidant reserve of pancreas (pancreatic-CL) and an increase in the lipid peroxidation products of pancreas (pancreatic-MDA).[41, 42] Prevention/reduction in the development of type 1 DM with SDG treatment was associated with reduction in WBC-CL, pancreatic-CL and serum and pancreatic MDA.[41, 42] Type 2 DM was associated with increases in oxidative stress as suggested by increases in the serum MDA.[43] The increases in the ROS could be due to a decreases in the levels of antioxidants. The elevated levels of ROS might damage the pancreatic β-cells leading to hyperglycaemia and glycosuria. SDG treatment reduced the serum levels of glucose and glycosuria. Hundred percent of untreated type 2 diabetic rats developed DM by the age of 72 days. Eighty percent of SDG treated type 2 diabetic rats did not develop DM by the age of 72 days suggesting that SDG prevented the development of DM by the age of 72 days. However, the rats which did not develop DM by 72 days of age, developed DM by 101 days suggesting that SDG treatment delayed the development of DM. These effects of SDG may be due to its antioxidant activity and its suppressive effect on PEPCK enzyme expression.

SDG is first hydrolysed and then metabolised to secoisolaricinol (SECO), enterodiol (ED) and enterolactone (EL) by gut microflora enzymes.[55, 56] Two questions arise: if SDG does not enter the circulation then how SDG is antidiabetic through its antioxidant activity and how it inhibits the PEPCK gene expression. The antioxidant activity of SDG could be through its metabolic products (SECO, ED, EL). Prasad[20] has reported that SECO, ED and EL are antioxidants. He also reported that antioxidant potency of SECO, ED and EL and SDG were 4.86, 5.02, 4.35 and 1.27, respectively compared to vitamin E. SECO, ED and EL were respectively 3.82, 3.95 and 3.43 times more potent than SDG. The other question arises as to how SDG can affect the PEPCK gene expression in liver and kidney if it cannot enter the circulation. Prasad[31] has reported that SDG suppressed the PEPCK gene expression. In this study SDG was added in hepatic cell culture.[57] This suggests that SDG can directly act on the PEPCK gene in liver. The effects of SDG metabolites on PEPCK gene expression are not available in literatures. The possibility exists that SDG supresses PEPCK gene expression.

Very limited studies are available in literature on the effects of FLC in type 2 DM in human. Studies of pure SDG on type 1 and type 2 DM in human are nil. A well-designed, randomised, placebo-controlled, multicentre clinical trials are needed for evaluating the efficacy, long-term safety and optimal dose schedules of SDG and FLC in humans. The problem might arise because of the unavailability of pure SDG.

Conclusion

In conclusion, oxidative stress is involved in the development of animal models of human type 1 and type 2 DM. SDG could prevent / reduce the development of type 1 DM and delay the development of type 2 DM. The reduction in the development of type 1 and type 2 DM could be due to the antioxidant and suppressive effect on the PEPCK enzyme. Beneficial effects of FLC in type 2 DM may be due to the SDG content in FLC. FLC lowers the levels of serum glucose and HbA_1c in type 2 DM in humans.

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None.

Conflict of interest

None.

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