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Assessment of antidiabetic and antioxidant activities of Cassia angustifolia and Feoniculum vulgare in diabetic rats

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ABSTRACT

Diabetes mellitus (DM) has become one of the most challenging health problems of the 21st century. It is associated with a number of different metabolic abnormalities. The use of herbs as medicines has increased all over the world, to maintain the target glucose level and modulate the oxidative stress associated with DM which would be an alternative approach for managing DM complications. The present work was conducted to test the hypothesis that combined treatment with aqueous extract of Cassia angustifolia (EACA) and Feoniculum vulgar(EAFV) that is more effective than each of them alone in improving the severity of DM and oxidative stress in streptozotocin-induced diabetic male rats. Diabetes was induced in male albino rats by an intraperitoneal injection of a single dose of streptozotocin (60 mg/kg body) .Fifty male albino rats, weighing 150±200 g, were divided into five groups, namely control, diabetic and diabetic rats received either EACA (150 mg/kg /day), or EAFV (150mg/kg/day) and their combination by gastric intubation for 4 weeks. Diabetic rats exhibited many symptoms, including loss of body weight, hyperglycemia, decreases in serum insulin, and high density lipoprotein-cholesterol levels, elevated triglycerides, total cholesterol , low density lipoprotein-cholesterol concentrations and liver marker enzymes. Significant increase in TBARS,(lipid peroxidation marker) was observed in diabetic liver and pancreas. This was accompanied by a significant decrease in GSH content, SOD and CAT activity of the liver and pancreas. Daily oral ingestion of EACA and/or EAFV extract for 4weeks after diabetes induction ameliorated hyperglycemia, increased insulin, improved lipid profiles, restored body weight loss and liver function, blunted the increased in MDA, modulated the levels of hepatic and pancreatic SOD and CAT activities and GSH content. It could be suggested that each of EACA and /or EAFV could be used as an antidiabetic compliment in case of DM. This may be related to their antioxidative properties.

Key words:*Streptozotocin-induced diabetic rats, Cassia angustifolia ,Feoniculum vulgare, Antioxidants,*

INTRODUCTION

The increasing worldwide incidence of Daibetes Mellitus (DM) in adults constitutes a global public health burden. Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both, so that glucose in the blood cannot be absorbed into the cells of the body [1]. The most common acute complications associated with diabetes include diabetic cardiomyopathy, neuropathy, nephropathy, retinopathy, coronary artery and peripheral vascular diseases [2].

IDF (2015) [3] estimated that globally 415 million of adults are living with diabetes and there are 318 million adults with impaired glucose tolerance, which puts them at high risk of developing the disease in the future. Saudi Arabia, currently ranked seventh among the top 10 countries known for their high prevalence of diabetes globally [4]. To treat DM, the number of synthetic drugs is available, but unfortunately adverse effects associated with the use of these medications have a number of complications. In recent years, there has been renewed interest in the treatment of diabetes using herbal drugs. The major advantages of herbal medicine seem to be their efficacy, low incidence of side effects, and low cost [5].

More than 400 plants with glucose lowering effect are known [6] . Fennel is one of the important spices that cure many diseases. Fennel (*Foeniculum vulgare*) is a plant species in the genus *Foeniculum*. It is highly aromatic and flavorful herb with culinary and medicinal uses, and is one of the primary ingredients of absinthe [7]. It is a hardy, perennial, umbelliferous herb, with yellow flowers and feathery leaves, growing wild in most parts of Europe, but is generally considered indigenous to the shores of the Mediterranean (botanical.com) [7]. Phytochemical studies have shown the presence of numerous valuable compounds, such as volatile compounds, flavonoids, phenolic compounds, fatty acids, and amino acids [8]. Fennel contains 90% trans anethole, up to 20% fenchone and also contains small amounts of limonene, camphor, alphapinene and about six additional minor volatile compounds [9]. A series of studies showed that *F.vulgare* has antioxidant, antitumor, chemopreventive, cytoprotective, hepatoprotective, and hypoglycemic activities [10][11][12][13][14].

Senna (*Cassia angustifolia Vahl*.) is a traditional medicinal plant belonging to the family *Leguminosae*. It is commonly known as sennamakkai or cassia senna. *C. angustifolia* is native to Saudi Arabia, Egypt, and Yemen. There are a number of species of Senna used throughout the world for medicinal purposes [15]. The historical significance of the *C. angustifolia* belongs to an ancient and blessed city Makkah where Prophet Muhammad (Peace Be Upon Him) firstly used it as an herbal medicine [16]. Senna is considered to be a remedy as a cleanser of the digestive system and tonic for the entire body. The Holy Prophet Muhammad (PBUH) said; “If there is any remedy against death, it is Sana, the gladdened, the graceful one” [17].

Cassia species are well known in folk medicine for their laxative and purgative uses [18] [19]. Besides, they have been found to exhibit anti inflammatory, antioxidant [20], hypoglycemic [21], anti plasmodial [22], larvicidal [23], antimutagenic [24] and anticancer activities [25]. They have been recommended for constipation, piles, epilepsy, respiratory diseases, skin infections, migraine and heart diseases [26].

Therefore, the present study was attempted to evaluate the antidiabetic and antioxidant activities of *Cassia angustifolia* and/or *Feoniculum vulgar* in streptozotocin-induced diabetic male rats.

MATERIALS AND METHODS

Plant material

The leaves of *Cassia angustifolia* and seeds of *Feoniculum vulgare* were purchased from the local traditional market in Jeddah, Saudi Arabia

Chemicals

Streptozotocin (STZ) was obtained from Sigma Chemical Company, Saint Louis, in Missouri, USA.Kits for insulin determination was obtained from Immunospec Corporation (USA), other chemicals and reagents used were obtained from biodiagnostic Chemical Company (Egypt).

Experimental Animals

Fifty adult male Albino rats weighing 150 to 200 g were obtained from the King Fahad Medical Research Center which were used as experimental animals. The animals were housed in cages and received normal rat chow and tap water ad libitum in a constant environment (room temperature 28 ± 2◦C, room humidity 60±5%) with a 12 h light and 12 h dark cycle. The animals were kept under observation for two weeks prior to the start of the experiments. Animal procedures were performed in accordance with the Ethics Committee of the King Fahad Medical Research Center and in accordance with the recommendations for the proper care and use of laboratory animals.

Preparation of the herbal extracts

The leaves of *Cassia angustifolia* and seeds of *Feoniculum vulgare*were grinded with a grinder. The powder (100 g) of each herb was extracted in 400 ml distilled boiled water in 30 min. The complex was filtered with Whatman No1 filter paper, then transmitted from the strainer and centrifuge with 3500 rpm for 20 min. After that, the extracts were concentrated in a hot water bath at 80^{o}C for 5 h. The filtered extract was then refrigerated at 5^{o}C until being used [27] .

Induction of Experimental Diabetes

Streptozotocin (STZ) was used to induce diabetes in rats by a single intraperitoneal injection at a dose of 60 mg/kg body weight [28] . STZ was freshly prepared by dissolving it in citrate buffer (0.5M, pH 4.5). Three days after STZ injection, fasting blood glucose (FBG) level was measured by using OneTouch Select Analyzer (LifeScan, Inc., UK) and rats having FGB level less than 200 mg/dl were discarded from the study.

Experimental Design

Fifty animals were used and divided into five groups of ten rats each as follows:

Group 1(Control): Animals were administrated with citrate buffer (0.01M, pH 4.5). The vehicle was administered orally for 30 days. This group served as normal control.

Group 2(Diabetic): Animals were given a single dose of STZ (60 mg/kg body weight, Intraperitoneal, i.p). The vehicle was administered orally for 30 days. This group served as diabetic control.

Group 3(Diabetic +AECA): The STZ induced diabetic rats were given *cassia angustifolia* aqueous extract (150 mg/kg body weight) by oral gavage for 30 days [29].

Group 4(Diabetic +AEFV): The STZ induced diabetic rats were administered with *Feoniculum vulgare* aqueous extract (150 mg/kg body weight) by oral gavage for 30 days [30].

Group 5(Diabetic +AECA+AEFV): The diabetic rats received an aqueous extract of mixture from *Cassia angustifolia* (150 mg/kg) and *Feoniculum vulgare* (150 mg/kg) by oral gavage for 30 days.

Blood collection and serum separation

At the end of the experimental period (4 weeks), rats were fasted overnight before scarification. Blood samples were withdrawn by heparinized capillary tube from the retro orbital plexu of each rat under anesthesia with diethyl ether, then were centrifuged at3000 rpm for 10 min to separate serum,which were stored at -20° C until biochemical analysis. Immediately after blood sampling, animals were sacrificed and the liver and pancreas of each animal was dissected and homogenized (1g/10ml ice-cold potassium chloride, 150 mM). The homogenate was then used for determination of the levels of reduced glutathione (GSH), thiobarbituric acid reactive substance (TBARS), and the activities of superoxide dismutase (SOD),catalase (CAT) and glutathione peroxidase (GPx).

Assay of Biochemical Parameters

Serum glucose was measured by enzymatic kits according to Kunst et al., [31]. Serum insulin levels were determined by solid phase enzyme-linked immunosorbent assay using Immunospec Insulin Quantitative Test Kit model E29-88. Total cholesterol was estimated by the method of Stadtman [32], triglycerides were estimated by the method of Rifai et al., [33], LDL-C was measured according to Gotto, [34] and HDL-C were measured as described by Warnick et al., [35]. The activity of aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALP) were measured as described by Bergmeyer et al., [36], Bergmeyer et al., [37] and Bowers and McComb, [38] respectively. The hepatic and pancreatic Lipid peroxidation was determined by measuring thiobarbituric acid reactive substance (TBARS) according to the method of Ohkawa et al., [39]. GSH was assayed according to Beutler et al., [40]. SOD and CAT were measured by the methods of Nishikimi et al., [41] and Aebi, [42], respectively. GPx was assayed according to Paglia and Valentaine [43].

Statistical analysis:

The data of each group were analyzed using the Statistical Package for Social Sciences (SPSS) version 20. The data were expressed as arithmetic mean and standard deviation of the mean (SD). The differences between groups were analyzed using one way analysis of variance (ANOVA), least significant difference (LSD) equation for parametric parameters. A P value less than or equal 0.05, was considered significant.

RESULTS

Induction of diabetes in the group (G2) exhibited highly significant (P<0.001) increase in blood glucose with a significant decrease in serum insulin levels as compared to control group (G1). Treated the diabetic rats with aqueous extracts of *Cassia angustifolia* and/or *Foeniculum vulgare*in G3, G4 and G5, reversed the above biochemical changes respectively as compared with the untreated diabetic group (Table 1).

Table1: Effect of aqueous extracts of *Cassia angustifolia* and /or *Foeniculum vulgare* on blood glucose and insulin levels in STZ-induced diabetic rats.

Groups / Variable	Control	Diabetic	Diabetic +AECA	Diabetic +AEFV	Diabetic +AECA +AEFV
Glucose (mmol/L)	4.16± .275	24.48±1.79 ***	6.92±.68 *** ###	6.99±.61 *** ###	5.67±.43 *** ###
Insulin (µU/ML)	9.18±.23	3.28±.25 ***	5.92±.07 *** ###	6.19±.25 *** ###	8.10±.22 *** ###

Each value represents means ± SD of 10 determinations.

***P < 0.001 as compared to control group.

P < 0.001 as compared to the untreated diabetic group.

Diabetic rats exhibited a significant increase in serum AST, ALT and ALP activities compared to controls (Table 2). Oral administration of AECA and/ or AEFV for 30 days significantly restored the enzyme levels to near normal (Table2). Moreover, the combined treatment of AECA and AEFV was more effective in preventing alteration in liver function.

Table2: Effect of aqueous extracts of *Cassia angustifolia* and /or *Foeniculum vulgare* on Serum levels of AST, ALT and ALP in STZ-induced diabetic rats.

Groups / Variable	Control	Diabetic	Diabetic+ AECA	Diabetic +AEFV	Diabetic +AECA +AEFV
AST (U/L)	31.45±2.36	93.35±4.22 ***	40.92±.70 *** ###	40.91±.67 *** ###	37.05±1.01 *** ###
ALT (U/L)	17.86±2.4	88.30±5.42 ***	53.25±5.47 *** ###	44.60±4.51 *** ###	41.50±5.68 *** ###
ALP (U/L)	46.85±	139.50± ***	73.78± *** ###	61.45± *** ###	59.16± *** ###

Each value represents means ± SD of 10 determinations.

***P < 0.001 as compared to control group.

###P < 0.001 as compared to the untreated diabetic group

The level of TC, TG and LDL-C in serum was significantly higher ($p<0.001$) in the diabetic group than that of the control group. Treatment of diabetic rats with AECA and/ or AEFV significantly ameliorated the elevation in the levels of lipid profile (Table 3). On the other hand, significant decrease ($p<0.001$) in serum HDL-C level was observed in diabetic group. This effect was significantly prevented by treatment with AECA and/ or AEFV (Table 3).

As shown in (Table 4), there were highly significant increases ($P<0.001$) in the hepatic and pancreatic TBARs accompanied by a highly significant decrease ($p < 0.001$) in the hepatic and pancreatic CAT, GSH , Gpx and SOD in the diabetic rats compared with the normal control rats. Treatment with AECA and /or AEFV produced a significant reduction in TBARS levels with significant increased in CAT, GSH, Gpx and SOD as compared to diabetic untreated rats.

Table3: Effect of aqueous extracts of *Cassia angustifolia* and /or *Foeniculum vulgare* on lipid profile in STZ-induced diabetic rats.

Groups / **Variable**	**Control**	**Diabetic**	**Diabetic+AECA**	**Diabetic+AEFV**	**Diabetic+AECA +AEFV**
Cholesterol (mmol/L)	2.31±.49	7.65±.86 ***	4.47±.51 *** ###	4.40±.59 *** ###	2.93±.49 ###
Triglyceride (mmol/L)	1.38±.09	5.3±.91 ***	2.33±.25 *** ###	2.34±.27 *** ###	1.58±.35 ###
LDLC (mmol/L)	.24±.06	5.84±.53 ***	2.23±.40 *** ###	2.26±.41 *** ###	.95±.23 *** ###
HDLC (mmol/L)	1.41±.14	.44±.09 ***	1.04±.15 *** ###	.97±.13 *** ###	1.30±.16 ###

Each value represents means ± SD of 10 determinations.
***P < 0.001 as compared to control group.
###P < 0.001 as compared to the untreated diabetic group.

Table4: Effect of aqueous extracts of *Cassia angustifolia* and /or *Foeniculum vulgare* on hepatic and pancreatic antioxidants in STZ-induced diabetic rats.

Groups / Variable	Control	Diabetic	Diabetic+AECA	Diabetic+AEFV	Diabetic+AECA +AEFV
TBARs (mmol/g) Liver	1.24±.23	6.07±.55 ***	2.35±.34 *** ###	2.52±.38 *** ###	2.11±.23 *** ###
Pancreas	1.15±.17	5.04±.54 ***	2.41±.09 *** ###	2.56±.08 *** ###	2.03±.16 *** ###
CAT (u/g) Liver	91.72±1.74	45.9±4.31 ***	78.71±2.58 *** ###	80.31±1.31 *** ###	85.0±1.47 *** ###
Pancreas	26.61±1.11	7.84±1.30 ***	19.70±1.36 *** ###	20.28±1.24 *** ###	22.58±1.45 *** ###
GSH (mg/g) Liver	31±1.16	10.49±.60 ***	21.51±1.37 *** ###	23.91±1.35 *** ###	27.14±.91 *** ###
Pancreas	30±1.92	8.34±.67 ***	22.91±1 *** ###	23.56±.58 *** ###	25.56±1.11 *** ###
Gpx (mu/ml) Liver	1779.31±16.16	746.61±15.88 ***	1530.14±17.75 *** ###	1573.66±4.46 *** ###	1651.42±4.43 *** ###
Pancreas	711.79±1.94	202.37±2.34 ***	505.18±3.95 *** ###	510.72±1.61 *** ###	684.28±3.56 *** ###
SOD (U/gm) Liver	4219.3±10.11	2495.8±3.91 ***	3298±2.26 *** ###	3293±2.75 *** ###	3897.2±6.60 *** ###
Pancreas	7964.9±34.74	4016.9±12.21 ***	5900.7±5.50 *** ###	5888.2±6.22 *** ###	6596.5±4.01 *** ###

Each value represents means ± SD of 10 determinations.

***P < 0.001 as compared to control group. ###P < 0.001 as compared to the untreated diabetic group.

DISCUSSION

Diabetes mellitus is a complex metabolic disorder that results from an absolute or relative deficiency of insulin with or without insulin resistance [44]. Medicinal plants are important sources of biologically active natural products which due to their curative properties, have been studied for many years [45]. The present study was designed to investigate the antidiabetic and antioxidant activities of *Cassia angustifolia* (senna) and/or *Feoniculum vulgare* (fennel) in diabetic rats.

In the present study, a single intraperitoneal (IP) administration of 60 mg/Kg streptozotocin induced a significant increase in fasting blood glucose accompanied with a significant decrease in serum insulin level. The increased fasting blood glucose in streptozotocin-induced diabetic rats due to destruction of insulin secreting pancreatic β-cells which lead to poor glucose uptake by peripheral tissues [46]. Administration of the aqueous extracts of senna and /or fennel to diabetic rats lowered blood glucose and ameliorated the insulin levels indicating that these extracts have hypoglycemic constituents. The hypoglycemic effect of senna reported in the present study is in agreement with previous reports [21] [47] [48]. This remark could be attributed to the role of senna by potentiating pancreatic secretion or increasing the glucose uptake [47]. In regard to the hypoglycemic effect of fennel, El-Soud et al., [14] and Parsaeyan [49] showed marked improvements of hyperglycemia and pathological changes induced by streptozotocin after fennel ingestion which can prove its effect as antidiabetic in folk medicine. Furthermore, Anitha et al., [7] suggested that the fennel exhibited the antidiabetic activity by decreasing oxidative stress, preserving pancreatic beta-cell integrity [50].

The hypoglycemic effect of fennel may be due to the presence of triterpenes, steroids, saponins and phenolic compounds [51], which stimulate insulin secretion through their antioxidant activities [52].

The liver is the main tissue for the detoxification and metabolism of most chemicals. Liver enzymes, including AST, ALT and ALP usually help to detect chronic liver disease by monitoring their concentrations [53] [54]. The results of the present study indicated that streptozotocin administration brought about a significant increase in liver marker enzymes. These results are in harmony with those of Assefa et al., [55].The increment of the activities of AST, ALT, and ALP in serum may be mainly due to the leakage of these enzymes from the hepatocytes into the blood stream, as a result of the hepatotoxic effect of STZ [56].

Results showing a significant reduction in serum levels of AST, ALT and ALP activities after oral administration of aqueous extracts of *C. angustifolia* , *F. vulgare* or the mixture of both, indicates the ability of these extracts to improve hepatic function. These improvements could be beneficial in preventing diabetic complications, as well as improving lipid and protein metabolism in diabetic liver. This finding is in agreement with that of (Hakkim et al., [57]; Farswan et al., [58]; Haidry and Malik, [59]). The hepatoprotective effect of *C. angustifolia* may be due to their containing of many important organic compounds such as sennosides and flavenoids [60]. Many studies demonstrated that the fennel plant has a hepatoprotective effect [59] [61] [62]. Moreover, Mhaidat et al., [63] reported that administration of the *F. vulgare* (100 mg/kg) extract attenuated the elevation of ALT and AST in diabetic rats, this may indicate that the extract is nontoxic and might protect liver complication associated with diabetes. The hepatoprotective action of fennel is due to the presence of D-limonene and β-myrcene compounds [64].

Lipids play an important role in the pathogenesis of diabetes mellitus. The high concentration of serum lipids in diabetes leads to the development of coronary artery disease in diabetic patients [65]. In the current results, STZ-induced diabetic rats had an elevation in the serum lipids. Similar results were obtained by several studies in experimental diabetes [66] [67] [68]. The abnormally high concentration of plasma lipids and lipoproteins pattern in diabetes mellitus is mainly due to the increase in the mobilization of free fatty acids from the peripheral depots, since insulin inhibits the hormone sensitive lipase [69]. Because insulin has a potent inhibitory effect on lipolysis in adipocytes, so the insulin deficiency depletes the activity level of lipoprotein lipase, thus leading to deranged lipoprotein metabolism during diabetes [70]. The increased levels of low-density lipoprotein (LDL) in the diabetic animals might be due to over production of LDL by the liver due to the stimulation of hepatic triglyceride synthesis as a result of the free fatty acid influx [71]. Studies by Khan et al., [72] have associated reduction in plasma HDL cholesterol in diabetic rats and diabetic patients to defect in reverse cholesterol transport. In the present investigation, treated diabetic rats with aqueous extracts of senna and/or fennel was significantly decreased the serum cholesterol, triglycerides, LDL and increased the HDL-cholesterol compared to their corresponding values in diabetic rats. The hypolipidemic effect of *Cassia angustifolia* was studied by many researchers [73] [74]. Extracts of various parts of the plant have been reported to possess hypolipidemic activity which may probably be due to the presence of flavonoids, triterpinoids and glycosides [73]. Treatment of diabetic rats with aqueous extract of fennel (*Foeniculum vulgare*) leads to the recovery of the lipid profile near the normal levels. This finding is in agreement with that of Anitha et al., [7] and Garg et al., [75]. The presence of t-anethol and flavonoids content in fennel may be associated with lowering total lipids, cholesterol, triglycerides and LDL-c levels.

Oxidative stress has been shown to play a role in the pathogenesis of diabetes, consequently; antioxidants may have a role in the alleviation of diabetes. Insufficiency of antioxidant defense system leads to elevation in the levels of free radicals. Elevated levels of free radicals may lead to disruption in cellular functions, oxidative damages to membranes and enhanced susceptibility to lipid peroxidation [76] [77]. Baynes and Thorpe [78] reported that hyperglycemia increases the generation of free radicals by glucose auto-oxidation and the increment in free radicals, thereby depleting the activity of antioxidant defense system and thus promoting de novo free radical generation that may lead to liver cell damage. Various tissues are more prone to oxidative damage and could result in various complications in long-term diabetes, implying that, the restoration of antioxidant status is an important parameter to evaluate the effect of antidiabetic compound [79].

The present study showed that diabetes-induced liver and pancreatic injuries were associated with increased amounts of lipid peroxidation (TBARs) and decreased antioxidant enzymes (GSH, SOD, CAT and GPx), indicating oxidative stress. The increased TBARS content in diabetic rats may be involved in the development of diabetic complications [80]. This increment in hepatic and pancreatic TBARs levels in the untreated diabetic rats may be associated with the destruction of erythrocytic membranes and tissues, caused by the oxidative stress [81]. SOD and CAT are the two scavenging enzymes that remove toxic free radicals [82]. The enzymatic antioxidant-catalase (CAT) is involved in the removal of hydrogen peroxide in living cells and protects against hydroxyl radicals toxicity. The antioxidant enzymes GPX and CAT are considered to be indicators of antioxidant status [83]. The depression of the activities of antioxidant enzymes obtained in the present study suggests an increased ROS generation in the untreated diabetic rats; and, therefore, increased oxidative stress [84]. In the present study, a

significant decrease in CAT activity in diabetic rats may reflect the inability of the liver and pancreas to eliminate hydrogen peroxide, a ROS.

The depletion of GSH level in diabetic rats might be due to its utilization to alleviate the oxidative stress in diabetes [85]. Therefore, the increased activity of GR in the diabetic rats was to compensate the decreased GSH levels through reduction of the oxidized glutathione (GSSG), which might be increased due to the presence of high levels of free radicals in DM [86].

Treatment of diabetic rats with senna and/or fennel reduced oxidative stress as evidenced by the restoration of the enzymatic antioxidative defense system. Other studies also support the antioxidant effect of senna extract [29] [87] [88]. The antioxidant ability of senna extract is mainly due to the presence of flavonoids [60]. Fennel has physiologic antioxidant activities including the radical scavenging effect, inhibition of hydrogen peroxides H_2O_2 and fechelating activities where it can minimize free radical which initiate the chain reactions of lipid peroxidation [89]. The antioxidant effect of *Foeniculum vulgare* was evaluated by Zaahkouk et al., [90] who showed a significant increase in GSH and CAT accompanied by a decrease in Malondialdehyde (MDA) in diabetic rats treated with fennel when compared with diabetic group. This may be due to the presence of phenols and flavonoids, which may have a major role in reducing oxidative stress associated with diabetes [7][49].

CONCLUSION

Senna *(C. angustifolia)*and/or fennel (*F.vulgare)* have an antioxidant effect which can decrease metabolic disturbances and oxidative stress that are associated with diabetes.

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