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Anti-hyperglycemic, cholesterol-lowering and HDL–raising effects of cumin (*Cuminum cyminum*) seeds in type 2 diabetes

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Abstract

Objective: To investigate anti-hyperglycemic, cholesterol-lowering and HDL-raising effects of cumin (*Cuminum cyminum*) seeds-a non toxic natural therapeutic agent, in type 2 diabetes. Materials and methods: The therapeutic effects of cumin seeds were evaluated by comparing with antidiabetic drug in type 2 diabetes patients. A total of 20, type 2 diabetes patients were divided into control and experimental groups consisting of 10 each and treated with anti-diabetic drug and cumin seed (commonly used spice) powder (5g/day) respectively for 60 days. Results: Patients with cumin seed therapy significantly improved their glycemic control as evidenced by significantly decreased levels of fasting glucose levels, showed significantly decreased levels of cholesterol (47%, $p<0.001$), triglycerides (26%, $p< 0.02$), plasma free fatty acids (4%, $p< 0.5$), phospholipids (9%, $p< 0.05$), LDL- cholesterol (5%, $p<0.5$),VLDL-cholesterol (26%, $p<0.02$) and atherogenic index (21%, $p<0.001$) while significantly increasing HDL-cholesterol (10%, $p<0.02$). Conclusion: *Cuminum cyminum* seeds exhibited anti-hyperglycemic, cholesterol-lowering and HDL–raising effects in type-2-diabetes and the efficacy of cumin seeds was proved to be superior to the drug in ameliorating the abnormalities in lipid profile in diabetes patients. This corroborates with earlier reports on experimentally induced-diabetic rats.

Key words: *Cuminum cyminum*, type 2 diabetes, anti-diabetic drug, glycemic control, lipid profile, lipoproteins.

1. Introduction

Diabetes mellitus is characterised by glycosuria, hyperglycemia and a disturbance in carbohydrate, fat and protein metabolisms and water and electrolyte balance [1]. According to recent estimates, the human population worldwide appears to be in the midst of an epidemic-diabetes. The World Health Organization predicts that the number of cases world wide for diabetes is now 150 million and will be doubled in coming years [2]. Lipid abnormality exists in 30% of diabetic patients and is presumed to be responsible for the increased risk of macrovascular disease in diabetes mellitus. Hypercholesterolemia is a common feature observed in diabetes certainly contributing to the high prevalence of accelerated atherosclerosis and coronary heart disease [3]. The common pattern of lipoprotein abnormalities found in type II diabetes consists of an increase

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in very low density lipoprotein cholesterol (VLDL-C), and low density lipoprotein cholesterol (LDL-C) and a decrease in high density lipoprotein cholesterol (HDL-C) [4].

Diet has been recognised as a corner stone in the management of diabetes mellitus [5]. A diet rich in fiber and low in fat particularly saturated fatty acids is currently recommended for the treatment of NIDDM to achieve better glycemic control and for lowering plasma LDL cholesterol. Spices form an important class of food adjuncts in human diet. Besides enhancing the taste and flavour of foods, spices exhibit a wide range of physiological and pharmacological properties [3]. *Cuminum cyminum* belonging to the family Apiaceae is widely used in ayurvedic medicine for the treatment of dyspepsia, diarrhoea and jaundice. In indigenous medicine, cumin seeds have long been considered stimulant and carminative, stomachic, astringent and are useful in diarrhea and dyspepsia [6]. Recent research indicates that oral administration (0.25g perkg body weight) of *Cuminum cyminum* for six weeks to alloxan diabetic rats resulted in significant reduction in blood glucose and an increase in total haemoglobin. It also resulted in a significant reduction in plasma and tissue cholesterol, phospholipids, free fatty acids and triglycerides. Moreover, supplementation of *Cuminum cyminum* was found to be more effective than commonly used sulfonyl urea drug- glibenclamide in the treatment of diabetes mellitus [7].

The above perspectives of *Cuminum cyminum*, the metabolic abnormalities associated with diabetes mellitus and lack of information on the influence of cumin seeds in diabetes patients, lead to the present study to assess the influence of cumin seeds on fasting blood glucose, serum lipid profile and lipoproteins in selected NIDDM patients and to compare with the data generated with control subjects treated with anti-diabetic drug.

2. Materials and methods

2.1 Procurement and preparation of sample

Cumin (*Cuminum cyminum*) seeds were procured from the local market of Anantapur, cleaned and finely powdered using electric grinder.

2.2 Feeding trails on experimental subjects

Preliminary information pertaining to age, diet, clinical complications, duration of diabetes and family history were collected with the help of a questionnaire. Based on the questionnaire, twenty NIDDM patients, aged between 40-60 years with no other complications were selected for this study and categorized in to two groups- control and experimental comprising of ten in each group. The experimental subjects were given 5g of cumin seed powder every day and the control subjects were on hypoglycemic drug (glipizide, 5mg/day) during the experimental period of 60 days. The consent of the subjects was obtained and the subjects were selected and treated strictly under the supervision of a diabetologist. Initially and at the end of experimental period, the following biochemical parameters were determined.

2.3 Biochemical analyses

Whole blood was drawn by vein puncture and disbursed into vials containing 5% EDTA as an anti-coagulant and centrifuged. The plasma was drawn using a sterile Pasteur pipette and expelled into a sterile labeled vials to be used for analysis and serum was collected without anti-coagulant. The following parameters were estimated at the initial and final stages of the experimental period. Fasting glucose [8] and free fatty acids [9] in plasma, cholesterol [10], triglycerides [11], phospholipids [12] and HDL cholesterol [13] in serum were estimated. LDL and VLDL cholesterol [14] and atherogenic index [15] were calculated.

2.4 Statistical analysis

Mean and standard error were calculated for the data. The data were statistically analysed by applying paired difference '*t*' test to assess the significant differences between initial and final values [16].

3.Results

3.1 Fasting glucose

Fig. I depicts fasting plasma glucose levels in control and experimental diabetics at the initial and final stages of experimental period. A significant ($p<0.05$) decrease (25%) in fasting glucose levels was observed in experimental diabetics i.e., treated with cumin seeds while such decrease was not observed in control subjects treated with the drug.

3.2 Lipid profile

Fig. 2, 3 and Table 1 represent various serum lipid parameters in control and experimental diabetics. Treatment with cumin seeds significantly decreased (47%, $p<0.001$) serum cholesterol (Fig.2), triglycerides (26%, $p<0.02$) (Fig.3), phospholipids (9%, $p<0.05$) and free fatty aicds (4%, $p<0.5$) (Table1) though the anti-diabetic drug decreased cholesterol by 8%, showed only 1 to 2% decrease with respect to other lipid parameters. Influence of cumin seeds on lipoproteins is presented in Fig. 5, 6, 7 which show a 5% and 26% ($p<0.5$ and $p<0.02$) decrease in LDL and VLDL cholesterol levels respectively in experimental subjects given cumin seeds. In addition, cumin seeds showed a significant increase (10%, $p<0.02$) in HDL cholesterol levels (Fig.7) while drug treatment decreased HDL cholesterol levels by 3%. Also, cumin seed treatment decreased atherogenic index (21%, $p<0.001$) while drug treatment showed a 9% elevation in atherogenic index (Fig.4).

4. Discussion

4.1 Fasting glucose

Dietary cumin is reported to be beneficial in streptozotocin diabetic rats which represent type I diabetes. Its mode of action was assumed to be pancreatic [5]. But in the present study, cumin seeds could exhibit hypoglycemic effect in type II diabetes. Hence, it can be both pancreatic and extrapancreatic. Fibre present in cumin seeds (12%) could have contributed to the observed effect as fiber was reported to slow down stomach emptying, delay and attenuate the postprandial raise in blood glucose [17]. In addition, ascorbic acid [18] niacin [19], copper [20] and manganese [21] present in cumin seeds were reported to exhibit anti-diabetic effect.

Table 1. Serum phospholipids and free fatty acids in control and experimental diabetics

Parameter	**Control**		**Experimental**	
	Initial	**Final**	**Initial**	**Final**
Phospholipids (mg/dl)	461.00+26.52	456.40+27.89 (1)	427.92+27.69	387.42+20.30 ** (9)
Free fatty acids (mg/dl)	496.87±31.24	497.84±30.71	553.56±33.00	546.28±33.60 * (4)

Values of are mean ± SEM of ten subjects in each group.
Figures in parentheses indicate per cent increase / decrease, Superscripts * $p<0.5$; ** $p<0.05$ indicate significant difference between initial and final values

Fig.1. Fasting plasma glucose in control and experimental diabetics

Values are mean ± SEM of 10 subjects in each group
Comparison between initial and final values in each group *p<0.05

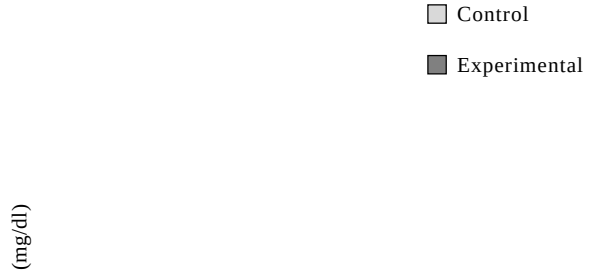

Fig.2. Serum cholesterol levels in control and experimental diabetics

Values are mean ± SEM of 10 subjects in each group
Comparison between initial and final values in each group *p<0.001

4.2 Lipid profile

4.3 Cholesterol

In this study, cumin seeds significantly decreased cholesterol levels in diabetic patients when compared to control group treated with drug. The hypocholesterolemic action of the spice in diabetics could be due to stimulation of hepatic cholesterol 7 α hydroxylase which brings about the conversion of cholesterol to bile acids as reported by Babu and Srinivasan [3] in curcumin fed STZ - diabetic rats. This hypocholesterolemic effect could also be due to saponins present in cumin seeds (0.4g/100gm) which prevent cholesterol absorption, interfere with its enterohepatic circulation and increase its fecal excretion [22]. It is possible that this spice would have regulated the activity of HMG CoA reductase, the key enzyme in cholesterol synthesis similar to the action of lovastatin, mevastatin which are hypocholesterolemic drugs [3]. Detailed studies are warranted to explain this hypocholesterolemic effect of cumin seeds.

4.4 Free fatty acids

In poorly controlled type II diabetics, the influx of free fatty acids from adipose tissue to circulation is increased due to activated lipolysis. Treatment with cumin seeds decreased plasma levels of free fatty acids but to a lesser extent. However, this decrease can be due to controlled lipolysis from adipose tissue as reported in insulin therapy by several researchers. The decreased levels of plasma free fatty acids improve insulin sensitivity resulting to improved glucose uptake [23].

Fig.3. Serum triglyceride levels in control and experimental diabetics

Values are mean ± SEM of 10 subjects in each group
Comparison between initial and final values in each group
*p<0.02

Fig.4. Atherogenic index in control and experimental diabetics

Values are mean ± SEM of 10 subjects in each group
Comparison between initial and final values in each group
*p<0.001

4.5 Phospholipids

A significant decrease in serum phospholipids was observed in experimental group treated with cumin seeds whereas in drug treated group, the decrease was minimum (1%). Serum phospholipids bear a close relationship with serum cholesterol. The changes that occur in lipid levels of plasma in diabetes, disturbs the equilibrium of various lipids of the cell membrane [24]. Cumin seeds by decreasing the elevated cholesterol and phospholipids in serum may contribute to maintain the equilibrium of various lipids of the cell membrane.

4.6 Triglycerides

In the present study, a significant decrease was seen in serum triglycerides in cumin-treated diabetics while drug-treated diabetics showed an insignificant increase (Fig.3). Hypertriglyceridemia is due to increased flux of free fatty acids into liver [25]. Fatty acids will be converted to triglyceride if their oxidative pathway is inhibited [26]. By decreasing free fatty acid content, as observed in this study, cumin seeds would have decreased the production of triglycerides.

4.7 Lipoproteins

4.7.1 LDL- cholesterol

Increased LDL-cholesterol was observed in some groups of diabetics. Glycosylation of LDL in type II diabetes may accelerate its deposition in vessel walls resulting in decreased LDL clearance [27]. Cumin seeds by decreasing blood glucose levels to normal, could have to some extent regularized LDL metabolism i.e., by decreasing the per cent of glycosylation of LDL, it contributed to increased clearance of LDL and thereby decreased deposition in

Fig.5. LDL-cholesterol levels in control and experimental diabetics

Values are mean ± SEM of 10 subjects in each group
Comparison between initial and final values in each group
*p<0.5

Fig.6. VLDL-cholesterol levels in control and experimental diabetics

Values are mean ± SEM of 10 subjects in each group
Comparison between initial and final values in each group
*p<0.02

vessel walls. Cumin seeds by exhibiting hypocholesterolemic effect, lowered LDL levels as HMG-Co A reductase inhibitors were reported to lower LDL levels and reduce the risk of cardiovascular diseases in diabetes as reported by Grundy [19]. A marked decrease in LDL levels in cumin seed-treated diabetics could be due to receptor mediated removal of LDL as some hypocholesterolemic drugs decrease LDL presumably by stimulating receptor mediated removal of LDL as reported by Babu and Srinivasan [3].

Treatment of diabetic dyslipidemia with niacin is a logical choice because the drug directly affects the main lipoprotein and lipid disorders observed in diabetes. Niacin blocks fatty acid flux from adipose tissue. It also suppresses hepatic assembly and release of VLDL. This later effect reduces fatty acid triglyceride levels and decreases number of small, dense LDL particles [28]. Niacin present in cumin seeds (2.4/100gm) [29], could have contributed for the same effect resulting in decreased levels of triglyceride and LDL.

4.7.2 VLDL-cholesterol

Cumin seeds have shown a tremendous decrease (26%) in VLDL levels by decreasing triglyceride levels as elevated plasma triglyceride in diabetes is reported to be associated with VLDL. This decrease is also due to increased clearance of VLDL. Improved glycemic control is reported to be associated with fall in VLDL production [30]. So as so, the glycemic control achieved by cumin seeds could have caused a fall in VLDL – production. Hence, cumin seeds would have either reduced VLDL production or enhanced VLDL clearance as reported by Andallu *et al* [31] in mulberry therapy.

Fig.7. HDL-cholesterol levels in control and experimental diabetics

Values are mean ± SEM of 10 subjects in each group
Comparison between initial and final values in each group
*p<0.02

4.7.3 HDL-cholesterol

HDL cholesterol concentration is reported to be lower in NIDDM as glycosylation of HDL accelerates its catabolism as reported in guinea pigs [32]. By controlling blood sugar levels, cumin seeds could have controlled glycosylation of HDL, thereby reducing catabolism and improving HDL levels. Normalization of hyperglycemia by cumin seed treatment could have decreased the activity of hepatic lipase, resulting in improved HDL levels. Role of niacin present in cumin seeds cannot be ruled out in elevating HDL levels as niacin may block a putative HDL holoparticle catabolic receptor responsible for intrahepatic degradation of HDL, thereby increasing the effective half life of HDL and raising HDL-cholesterol concentrations. Niacin is the most potent drug currently available to raise HDL-cholesterol levels [19].

4.6.4 Atherogenic index

Atherogenic index is a ratio of total cholesterol and HDL- cholesterol. Elevated LDL, VLDL and decreased HDL-cholesterol concentration in diabetics appear to be altered favourably by cumin seed treatment and almost all the lipid abnormalities developed in diabetes were effectively counted by cumin seeds. Certain specific phytochemicals such as polyphenols (1.45 mg/100g), tannins (300mg/100g), saponins (400mg/100g) and fiber present in (12gm/100g) cumin seeds might be playing a role in rectifying lipid abnormalities. The precise mechanism underlying this effect though is complex, most of these compounds were reported to inhibit absorption of lipids from the intestines.

Non enzymatic antioxidants (carotenoids, vit. C and E, and polyphenols) present in dietary supplements are capable of modulating LDL oxidation, normalise the elevated LDL-cholesterol and thereby reduce the risk of development of atherosclerosis in diabetes [47]. The anti-oxidants and other compounds present in cumin seeds also acted in the similar way to normalize lipid abnormalities in diabetics whereas alterations in lipid profile could not be normalised in control subjects treated with the drug. This study warrants further investigation to isolate the bioactive principles and to determine their mode of action.

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