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IN-VITRO ANTIOXIDANT AND ANTIDIABETIC ACTIVITY OF CUMINIC ACID

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ABSTRACT: Diabetes mellitus is a metabolic disorder caused due to lack of insulin and/or its insufficiency. It is ranked ninth among the leading causes of death globally. As Oral hypoglycemic agent usage causes one or more side effects, phytochemicals can be used as alternative herbal medicine to treat diabetes mellitus with little or no side effects. In the current study, Cuminic acid was evaluated for its antioxidant and antidiabetic activities under *in-vitro*. Different doses of Cuminic acid were used to analyze free radical scavenging effect by DPPH, H_2O_2 & NO methods. α- amylase and α- glucosidase inhibitory effects were studied using various doses of Cuminic acid. Glucose diffusion inhibitory assay was carried out using a Dialysis bag. In the results of the antioxidant study, Cuminic acid showed the highest free radical scavenging activity in all the methods compared to standard Ascorbic acid. Enzyme inhibition studies also showed significant increase in antidiabetic activity indirectly with increasing concentrations of Cuminic acid, which was found to be equivalent to the standard drug acarbose. Glucose diffusion inhibitory assay also proved significant compared to the standard metronidazole drug. The study's results substantiate that Cuminic acid has potent *in-vitro* antioxidant and antidiabetic activity.

INTRODUCTION: The production of highly reactive species known as free radicals (ROS/RNS), are triggered by various metabolic reactions in the human body, which cause the oxidation of cellular machinery through the transfer of their free unpaired electron [1]. Although oxidative processes, particularly those catalyzed by decompartmentalized transition metals, are linked to diabetes mellitus, their causal relevance in diabetic tissue damage is unknown [2, 3]. Free radicals in excess damage all the vital elements of cells leading to death.

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The main source of them is thought to be glucose oxidation. In enediol state, glucose is oxidized to produce an enediol radical anion, which is then converted into reactive keto aldehydes and superoxide anion radicals *via* a transition-metal dependent process. Superoxide radicals dismutate to hydrogen peroxide in the presence of transition metals, which, if not destroyed by catalase or glutathione peroxidase, form extremely dangerous ÖH radicals [4].

Various enzymatic and nonenzymatic antioxidant processes can help remove reactive molecules [5]. Antioxidant supplementation is examined as adjuvant therapy in diabetics, with the idea that strengthening antioxidant defense will mitigate oxidative stress and assist halt or avoiding vascular alterations that cause serious problems [6]. Hyperglycemia is a symptom of diabetes mellitus, caused by a lack of insulin secretion or action, or

both by the pancreas [7]. Because of hyperglycemia and insulin resistance, people with T2DM are prone to develop microvascular complications (retinopathy, nephropathy, and neuropathy) and cardiovascular co-morbidities [8]. It has been projected that diabetes may affect 9.3% (463 million individuals) of the global population in 2019, rising to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045 [9]. Even though several types of oral hypoglycemic medications and insulin are available for treating diabetes mellitus, herbal therapies are gaining popularity due to the adverse effects associated with these therapeutic agents [10].

As a result, there is a growing desire for scientific confirmation of phytochemicals with antidiabetic potential and few or no negative effects. Plant-derived medications are gaining popularity in disease control/management because they are less expensive, more tolerable and have fewer side effects than traditional antihyperglycemic or antidiabetic medications. Natural products isolated from plants, as demonstrated with the discovery of "metformin" from *Galega officinalis* are important sources of medication. Strenuous scientific investigations to identify the different bioactive principles in managing diabetes mellitus should be prioritized to identify novel approaches for treatment and management [11].

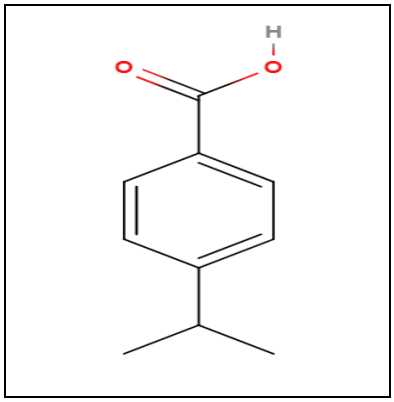

FIG. 1: CUMINIC ACID (4-ISOPROPYL BENZOIC ACID)

Cumin seeds (*Cuminum cyminum* L., Apiaceae) are used extensively as a spice and in traditional medicine to cure many ailments. Cumin's biological properties, which have been attributed to its bioactive elements such as terpenes, phenols, and flavonoids, have been well documented in the literature [12].

Cuminic acid (4-Isopropyl benzoic acid) **Fig. 1** is a monoterpene and one of the bioactive compounds of *Cuminum cyminum* seeds which constitute aldehyde (35-63%), cuminyl alcohol (3.5%), acidity on the basis of cuminic acid (0.36-1.8%) [13, 14]. Cuminaldehyde has been discovered to contribute to cumin's anti-diabetic properties. Cuminaldehyde had previously shown notable but lesser inhibitory effects on aldose reductase and alpha-glucosidase than standard oral antidiabetic drug acarbose [15].

Later, in 2013, Patil *et al.* reported that cumin aldehyde and cuminyl alcohol had glucose-dependent insulinotropic effects in diabetic rats, an effect mediated by inhibiting ATP-sensitive potassium channels and elevating intracellular calcium concentration in cultured rat pancreas cells. Cuminaldehyde also protected pancreatic cells from streptozotocin-induced cytotoxicity [16].

No scientific study has been conducted to validate Cuminic acid for its *in-vitro* antioxidant and antidiabetic activity. However, Cuminaldehyde and Cuminyl alcohol are experimentally evaluated for the same. Hence, in the present work, an attempt was made to study cuminic acid's antioxidant and antidiabetic potential under *in-vitro* conditions.

MATERIALS AND METHODS:

Chemicals and Reagents: Metronidazole; p-nitrophenyl-α-glucopyranoside (PNPG); Acarbose ; Cuminic acid; porcine α-amylase; α-glucosidase; Diphenyl-1-picrylhydrazyl (DPPH); Dialysis tubing membrane (MW12173) were purchased from Sigma Aldrich, USA. Soluble starch: Hi Media. All the chemicals and reagents were of AR.

DPPH Assay: CA's DPPH radical scavenging activity was tested, following the method of Blois [17] and Desmarchelier *et al*. [18].

Cuminic acid/Ascorbic acid was added to 3 ml of DPPH (0.004%) solution at concentrations ranging from 50µg/ml to 200µg/ml. Methanol was used as the control. At ambient temperature, the DPPH is violet in colour, but it turns yellow when exposed to hydrogen or when antioxidants donate electrons. After 30 minutes of incubation, the extinction was measured at 520 nm.

Hydrogen Peroxide Scavenging Assay: The potential of Cuminic acid for its radical scavenging was evaluated using H_2O_2 [19]. One ml of various concentrations of Cuminic acid and Ascorbic acid was added to 2 ml H_2O_2 solution (PBS, pH 7.4). The absorbance was measured at 230nm after 10 minutes. Control was developed same as above without test compound and standard.

NOS Assay: NO scavenging assay was performed with sodium nitroprusside [20] of the Griess Illosvoy reaction. 1 ml of CA at various concentrations was added to 10mM sodium nitroprusside (2 ml) in 0.5 ml phosphate buffer saline (pH 7.40) and incubated at 25°C for three hours. In the end, one ml of naphthyl ethylenediamine dihydrochloride (0.1% w/v) was added and incubated at room temperature for half an hour. The intensity of color was read at 546 nm. A blank/control was developed similarly without a test compound or standard. The percentage inhibition was calculated using the following equation:

% Inhibition = (Abs control – Abs test) / (Abs control) x 100

Inhibition Assay of α- Amylase: The *α*-Amylase inhibition assay was carried out by the method of G.L. Miller, (1959) [21]. Cuminic acid/acarbose (50µg/ml, 100µg/ml, 150µg/ml and 200µg/ml) were incubated for 10 minutes at 25°C with 500 µl of 20 mM sodium phosphate buffer (pH 6.8) with 20 µl of amylase (1U/ml). After pre-incubation, each tube was added with 1 ml of 1% starch solution in 0.02 M sodium phosphate buffer (pH 6.9) and incubated for 15 min. One ml DNS was added to arrest the reaction. After that, the tubes were kept in a boiling water bath for 5 min and cooled to room temperature. After that, distilled water (10ml) was added to the reaction mixture, and the absorbance was measured at 540 nm. The test compound was not used in the preparation of the control samples. The following formula was used to determine the percent inhibition of amylase activity:

% Inhibition = (Abs control – Abs test) / (Abs control)

Inhibition Assay of α- Glucosidase: The glucosidase inhibition assay was performed using the method of Kim *et al.* (2010) [22]. The different concentrations of compound and standard drug acarbose were prepared. Phosphate buffer (1 ml; 100mM, pH 6.8) and 80 µl of test compound / acarbose of concentrations (50 µg/ml, 100 µg/ml, 150 µg/ml and 200 µg/ml) were added to 20 µl of α-glucosidase and incubated at 37°C for 10 minutes. Later, pNPG- 50µl (5mM) was added to the assay mixture to initiate the reaction. Then, the reaction mixture was incubated at room temperature for one hour and arrested the reaction by adding 2.5ml of 0.1 M Na_2CO_3. The absorbance was measured at 400nm to determine the activity of α-glucosidase activity.

Glucose Diffusion Inhibition Assay: For evaluating the Cuminic acid's ability to stop glucose movement across a semi-permeable membrane, a model described by A.M. Gallagher *et al*, (2003) [23] was adopted. A dialysis tube sealed at one side (15 cm × 25 mm), was added with 2ml of 22mM D-glucose in 0.15 M NaCl, 1 ml test compound (1 mg/ml), and in control (water alone).

The opposite end was sealed and placed carefully into a beaker with 45 ml 0.15 M NaCl. It was transferred onto an orbital shaker incubator at 37°C at 100 rpm. 10 µl of the solution was collected at timed intervals, and glucose was determined in it using an Accu-Chek Active Glucometer (Roche, India). The concentration-dependent effect of Cuminic acid (50µg, 100µg, 150µg, and 200µg/ml) was evaluated for glucose diffusion inhibition against the standard drug metronidazole.

Statistical Analysis: The differences among mean values between groups were tested using one-way ANOVA with a post-hoc Tukey HSD test, and all tests were considered statistically significant at $p \leq 0.05$. The results are expressed as mean±SD.

RESULTS AND DISCUSSION: In diabetic patients, increased oxidative stress and decreased antioxidant levels have been linked to the development of various chronic co-morbidities [24].

An imbalance between radical generating and scavenging systems results in increased free radical production decreased antioxidant defense activity, or both [25]. According to current literature, obesity and under physical activity are the major risk factors for the onset of type 2 diabetes, caused due to increasing insulin resistance or decreasing insulin production [26].

It has been proposed that the following four main metabolic alterations generated by hyperglycemia are triggered by the same mechanism superoxide radical overproduction [27]. Firstly, elevated flux through the polyol pathway; secondly, enhanced glycosylation of proteins in blood; thirdly with increased activity of protein kinase C and finally with increased shunting of excess glucose through the hexosamine pathway. Antioxidants in the diet are intended to safeguard against the development of diabetes by suppressing peroxidation chain reactions in the body [28].

An adequate intake of antioxidants appears to play a potential role in preventing type 2 diabetes. Nevertheless, there is limited epidemiological evidence on the significance of dietary antioxidant consumption in type 2 diabetes prevention [29].

Antioxidants can be found in a variety of foods [30]. Cumin seeds (*Cuminum cyminum* L.) are frequently used as a spice in Indian cuisine because of their distinct aroma; they are also often used in traditional medicine to treat a variety of ailments.

Cumin's biological activities have been established due to occurrence of bioactive compounds such as terpenes, phenols, and flavonoids, according to a plethora of evidence in the literature [12]. Cumin seed essential oil is a very good source of natural antioxidants that could be used in food preservation and health promotion [31].

Monoterpene hydrocarbons have a higher antioxidant activity than sesquiterpenes and non-isoprenoid components. The antioxidant activity of many monoterpenes has been studied, and it has been discovered that none of them are more powerful than oxygenated monoterpenes [32].

Cuminic acid, a constituent monoterpene of essential oil of cumin seeds, shows very convincing antioxidant activity.

Free Radical Scavenging Activity (DPPH) of Cuminic Acid: The results presented in **Fig. 2**, demonstrate that at all the tested concentrations, Cuminic acid has a high free radical inhibitory capacity in the DPPH assay compared to the standard ascorbic acid. However, a twofold antioxidant activity was observed for Cuminic acid at 200µg/ml over the 50µg/ml.

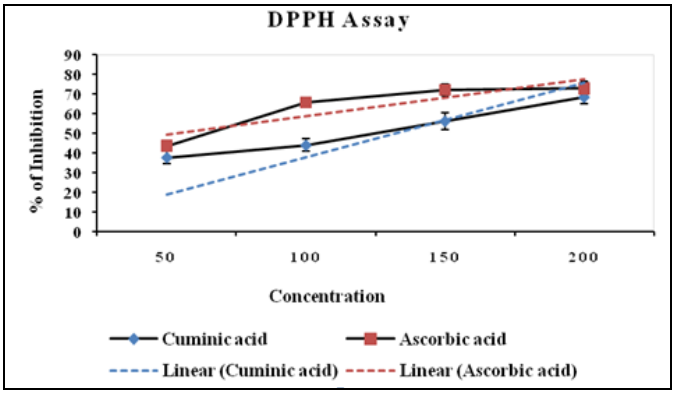

FIG. 2: DPPH RADICAL SCAVENGING ACTIVITY OF CUMINIC ACID. Values are expressed as mean ± SD

Nitric Oxide and H_2O_2 Scavenging Activity of Cuminic Acid: In the NOS assay **Fig. 3** and H_2O_2 scavenging assay **Fig. 4** also similar trend was observed with the free radical scavenging capacity of 44.6% and 33.21%, respectively at 200µg/ml when tested at a range of 50µg/ml to 200µg/ml.

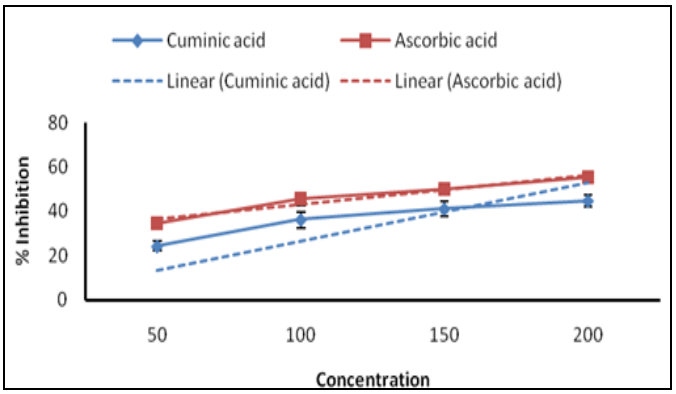

FIG. 3: NITRIC OXIDE SCAVENGING ACTIVITY OF CUMINIC ACID. Values are expressed as mean ± SD

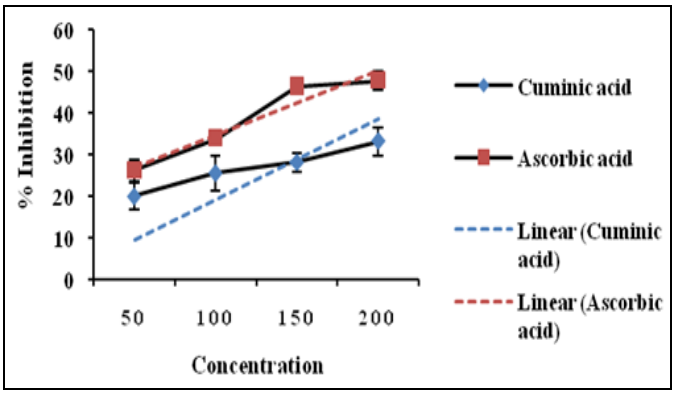

FIG. 4: H_2O_2 SCAVENGING ACTIVITY OF CUMINIC ACID. Values are expressed as mean ± SD

α- Amylase & α- glucosidase Inhibition Assay: α-amylase (EC 3.2.1.1) [33] hydrolyses glycosidic bonds of starch and glycogen [34]. It is ubiquitous in humans and other mammals [35]. α-glucosidase (EC 3.2.1.20), is a glucosidase of brush borders that acts

upon α(1→4) bonds [36] of starch and disaccharides to release free glucose. In diabetics, inhibiting alpha-amylase is an essential therapeutic target for regulating postprandial blood glucose elevations [37]. Inhibition of α-glucosidase and α-amylase can lower the post obsorptive rise in blood glucose and hence can be a better strategy in achieving the glycemic goals in diabetic and borderline prediabetics [38]. Plant-based alternative medications and functional foods that modulate physiological effects in preventing and treating diabetes and obesity are becoming more popular. The plant kingdom could be a vast resource for finding natural, effective oral hypoglycemic medicines with little or no adverse effects. Over 1200 plant species have been identified as being utilized effectively for hypoglycemic action over the world [39]. As a result, natural α-glucosidase and α-amylase inhibitors derived from the plant kingdom offer promising leads for hyperglycemia management [40]. In an alpha-amylase inhibitory assay with Cuminic acid at a concentration range of 50µg/ml, 100µg/ml, 150µg/ml, and 200µg/ml, shown inhibition effect in the percentage of 31.06, 45.28, 62.15 & 75.76 **Fig. 5** with an IC_{50} value of 122.72µg/ml in comparison with the standard antidiabetic drug acarbose with an IC_{50} value of 44.97µg/ml. The same trends of results were observed with the α-Glucosidase inhibitory study, suggesting that Cuminic acid has a potent inhibitory effect similar to the standard drug acarbose **Fig. 6.**

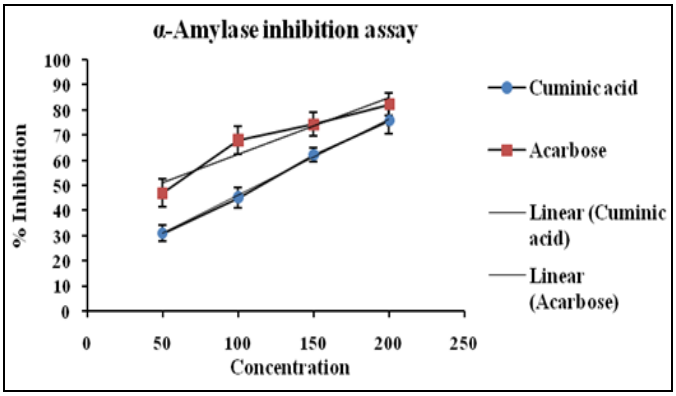

FIG. 5: α-AMYLASE INHIBITION ACTIVITY OF CUMINIC ACID. Values are expressed as mean ± SD

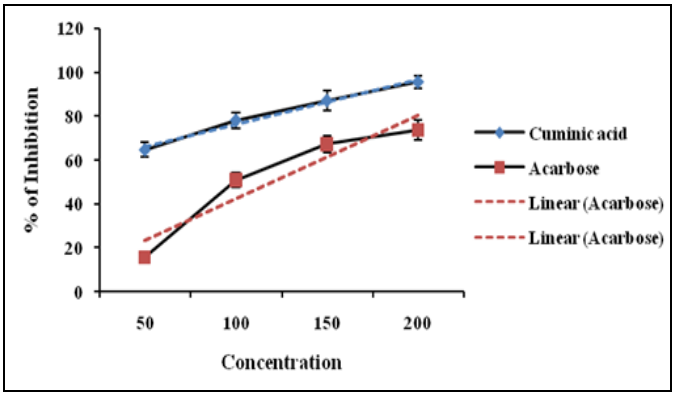

FIG. 6: α-GLUCOSIDASE INHIBITION ASSAY. Values are expressed as mean ± SD

Glucose Diffusion Inhibition Activity of Cuminic Acid: *In-vitro* antidiabetic activity screening approaches play a critical role in avoiding or limiting the use of experimental animals [41]. Both metabolic requirements of the tissue, as well as glucose availability, influence the mode of glucose uptake in different tissues. The intake of glucose occurs in two ways: assisted diffusion (a passive process) and active transport. In the glucose diffusion inhibition assay **Fig. 7**, glucose diffusion was inhibited strongly by the Cuminic acid over some time across the semi-permeable cellulose acetate membrane compared to the control and standard drug metronidazole.

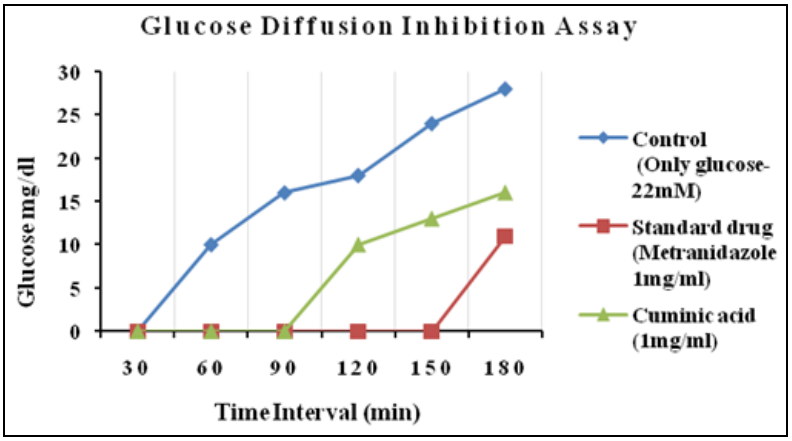

FIG. 7: GLUCOSE DIFFUSION INHIBITION ACTIVITY OF CUMINIC ACID. Values are expressed as mean ± SD

CONCLUSION: In conclusion, in our preliminary studies, Cuminic acid at 200µg/ml has a significant *in-vitro* α-amylase & α-Glucosidase inhibitory activity conferring indirect evidence for antidiabetic activity. The interactions between different constituents of Cumin oil may decrease the antioxidant potential. The antagonistic and synergistic activities may be the reason for such results [42]. The free radical inhibitory effect ascribed in this study demonstrates that Cuminic acid has potent antioxidant activity despite of its low constituent concentration in cumin seeds compared to the Cuminaldehyde and Cuminyl alcohol which are reported to have antioxidant and antidiabetic activity [43]. Cuminic acid, an acidic constituent of essential oil of cumin seeds [13,] which is scientifically underexplored for its potential biological activities, drags the attention and may be taken as a lead compound for the development of a safer and cost-effective therapeutic drug for the treatment of diabetes mellitus with little or no side effects. Further studies are recommended to evaluate its biological activities using various *in-silico* and *in-vivo* models. In our future studies, we are attempting to study the *in vivo* effects of toxicity and antidiabetic activities in experimental rats.

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CONFLICT OF INTEREST: The authors have no conflict of interest.

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