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Effect of *Curcuma longa* on glycemia, neuropathic sensation, and advanced glycation end product in diabetic patients

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Abstract: Diabetes is a chronic disorder affecting a large number of people throughout the world. According to the American Diabetes Association, overeating is the major diet-related risk factor for type 2 diabetes. To ensure the efficacy of *C. longa.* in the improvement of glycemic control, neuropathic sensation, and reduction in the formation of advanced glycation end products 90 people that meet inclusion criteria were divided into 2 groups, the control group was only given antidiabetic drugs without *C. longa* supplement and the treatment group were given *C. longa* supplement as well as recommended hypoglycemic drugs for 120 days. Results reveal that in all combinations of antidiabetic medicine the addition of curcumin has significantly reduced the level of hemoglobin A_1C as compared to the control group. Similarly, there has been a significant reduction in the formation of advanced glycation end products at the end of the study. While a significant improvement in neuropathic sensation has also been observed. Hence it may be concluded that *C. longa* can be efficiently used in chronic patients with diabetes as a supplement to manage the symptoms and complications of type II diabetes.

Keywords: *Curcuma longa*, diabetes, advanced glycation end products.

INTRODUCTION

The occurrence of diabetes in 2000 was 2.8% worldwide and it is expected to increase to 4.4% by 2030 (Ready, 2017). Obesity and a sedentary lifestyle seem to be the most common causes of type 2 diabetes (Wu *et al*., 2014) and are responsible for about 90% to 95% of diabetes cases in the United States. Fortunately, diabetes can be prevented or delayed by maintaining a healthy lifestyle and healthy body weight (Reddy, 2017; Galaviz *et al*., 2018). *C. longa* is a perennial herb that belongs to the family of ginger (Zingiberaceae) and is widely cultivated in the southern-west and southern tropical regions of Asia (Kocaadam & Sanlier, 2017). It is effective in various health issues due to a lipophilic polyphenol substance called curcumin (Tsuda, 2018). *C. longa* is used as a spice because of the color, flavor, and taste of the foods in many Asian countries. It is an important component of traditional Chinese Medicine and Indian Ayurvedic medicine (Baliga *et al*., 2015). Ayurvedic medicine documents its use in the treatment of asthma, liver disorder, dermatological preparation, rheumatism, diabetic wounds, runny nose, cough, and sinusitis (Prasad & Aggarwal, 2011). *C. longa* is recently recommended for its anti-cancer effects (Tomeh *et al*., 2019). It also possesses antioxidant and anti-inflammatory, properties that have a curial role in the prevention and treatment of various ailments such as neurological disorders, cardiovascular disorders, and diabetes (Tanvir *et al.,* 2017). The *C. longa* lowers the amount of glucose in diabetes as observed in animal studies (Rivera-Mancía *et al.,* 2015; Pivari *et al*., 2019) furthermore, it also weakens tumor necrosis by reducing the level of TNF-α and plasma free fatty acids. *C. longa* reduces the level of thiobarbituric acid and can activate the induction of peroxisome proliferator-activator receptor-gamma (Grarup *et al.,* 2014; Wong *et al*., 2016; Hosseini *et al.,* 2018).

C. longa can reduce the blood glucose level in diabetes (Pivari *et al.,* 2019). Oral use of *C. longa* can reduce body weight, and decrease blood glucose and glycosylated hemoglobin. It also improves insulin sensitivity as observed in the pre-diabetic population. *C. longa* when taken in diet also prompted effects on fasting blood glucose, urine sugar, and urine volume in streptozotocin-induced diabetic rats (Chougala *et al.,* 2012, Chuengsamarn *et al.,* 2012).

Most studies have been carried out to examine the effects of *C. longa* in animal models (Booth & Young, 2000; Gupta *et al.,* 2011; Aldebasi *et al.,* 2013; El-Bahr, 2013; Maradana *et al.,* 2013; Ghorbani *et al.,* 2014). Studies on the human model are infrequent and its effects on individuals have not been recognized. Therefore the current study has been designed to assess the outcome of *C. longa* on glycemic control, prevention, and reversal of diabetes-associated complications in humans.

MATERIALS AND METHODS

C. longa preparation

Fresh rhizomes of *C. longa* were purchased from the local market and identified by the Department of Pharmacy, Shaheed Mohtarma Benazir Bhutto University allocating the number Pharmacog/CU (Z)/ 002. The rhizomes were

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then cleaned with water to get rid of the debris and treated with steam for 10 minutes followed by drying in a hot air oven at 50°C for 8 hours after slicing the boiled rhizome. The collected dried rhizome was blended into a fine powder with a high-speed blender.

Study design and ethical approval

Before the start of the study, the Ethical Review Committee at Ziauddin University approved the study with reference code 3031220WAPHA dated 09th Mar 2021. The 90 person that meets the inclusion criteria were separated into 2 groups, the control group taking antidiabetic drugs lacking *C. longa* supplement and the treatment group taking *C. longa* supplement as well as recommended antidiabetic drugs. Depending on the hypoglycemic drugs, patients were further classified into sub-classes. 8 subjects each from the control and treated groups received metformin plus sitagliptin together, 17 subjects from each class received glimepiride, 30 subjects were kept on metformin and glimepiride and 5 subjects from the treated and control group were given insulin.

Before the start of the study, all the participants were briefed about the objectives of the study and filled out written consent. All contributors were educated to continue their lifestyle, physical activity, and hypoglycemic drugs are taken during the study, however, maintain their dietary intake to 1800 calories per day. This was confirmed by guidance at the beginning of the research and every visit. The contributors were also monitored every week on the telephone and directed to report any new symptoms to the investigator immediately after using the supplement. All the subjects of the treatment group meeting the inclusion criteria were directed to use a 1g *C. longa* powder capsule three times a day before each meal for 120 days along with recommended hypoglycemic drugs. Results were matched with the control group kept on hypoglycemic drugs lacking *C. longa* supplement.

Inclusion criteria

All of the participants in this study were adults with type II diabetes aged between 25 to 65 years and a Body Mass Index of 18.5-35 kg/m^{2}with diabetes for not more than ten years.

Exclusion criteria

Patients suffering from hemoglobinopathy, liver disease, type 1 diabetes, and non-diabetic subjects, while patients on multivitamin or mineral supplements or traditional drugs during the last three months were also not included in the study.

Sample collection

The blood specimens of all contributors were taken at the start of the study and after *C. longa* supplementation as per protocol. The ethylene diamine tetra acetic acid vials were utilized to collect blood specimens. Plasma was separated by centrifugation at 3000 rpm for 10 minutes and biochemical factors were determined in serum.

Determination of HbA_1C by High-performance Liquid Chromatography

The HbA1c level was determined using the D-10 hemoglobin A_1C testing system of Bio-Rad laboratories which used the ion-exchange high-performance liquid chromatography technique. The 1ml of whole blood sample was diluted automatically on D-10, then injected into the analytical cartridge. A programmed buffer gradient was delivered by D-10. The hemoglobin is separated due to ionic interaction with the material of the cartridge. The reference standard used was cation exchange chromatography # 1250562 containing 6 vials of a lyophilized mixture of equine myoglobin, Ribonuclease A, and cytochrome c supplied by Bio-Rad laboratories. The absorbance of the separated hemoglobin after passing through was measured at 415 nm. Analysis was done with D-10 software.

Neuropathic sensation with monofilament

10-gram monofilament is an instrument used to screen diabetic patients for loss of sensation. The patients were first briefed about the use of the instrument. It was ascertained that patient was not able to see the point where pressure was applied. The monofilament was warmed up by applying on the inner wrist to ensure the sensation when applied to different areas of the feet. The duration of its application from skin contact to the departure of monofilament was 2 seconds. The filament was pressed and the patient was asked about the sensation and an answer was noted in different areas of the feet as shown in fig. (1).

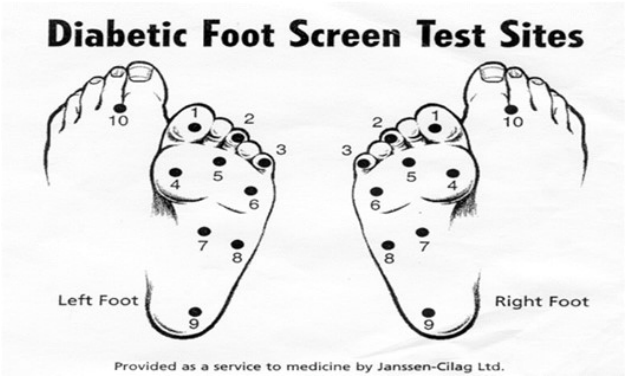

Fig. 1: Diabetic Foot Screen Test

Loss of protective sensation = No feeling in less than 8 sites

Advanced glycation end products measurement method

Human Carboxy-methyl-lysine (CML), an Enzyme-Linked Immunosorbent Assay kit from the Bioassay Technology laboratory was used for the measurement of advanced glycation end products. Already prepared sample, reagents and the standard solution were brought to room temperature for analysis as an assay has to be

performed at room temperature. 50 microliter of the standard solution was placed in the standard well, 40 microliters of sample were added to the sample well along with 10 microliters of CML antibody followed by the addition of 50 microliters of streptavidin-HRP to both standard and sample well. Incubation was then carried out at 37 °C for 60 minutes after covering the plate with a sealer. After 60 minutes, the sealer was removed and the plate was washed 5 times with buffer. 50 microliters of substrate solution A were added to each well followed by the addition of 50 microliters to substrate solution B. 50 microliter of stop solution was then added which change the color from blue to yellow immediately. Optical density was determined with the help of a microplate reader set to 450 nm.

STATISTICAL ANALYSIS

All the outcomes were evaluated by SPSS version 20. The numbers were shown as a mean and standard error to the mean. One-way analysis of variance was followed by the least significant change to relate the importance of biochemical factors. The p-value difference of less than 0.05 was deliberated substantial while the value of less than 0.01 was reflected as highly substantial.

RESULTS

Effect on HbA1c

The present study reveals that the curcumin supplement along with standard anti-diabetic treatment showed highly significant improvement of HbA_1C in sitagliptin + Metformin, glimepiride + metformin, and glimepiride treatment groups as compared to control groups. However, the insulin treatment group also revealed a significant decrease in HbA_1C.

Table 1 compare HbA_1C in treatment (antidiabetic drugs + curcumin) and the control group was given antidiabetic drugs only. After 120 days in groups treated with sitagliptin + metformin, glimepiride + metformin, and glimepiride along with curcumin supplement there was a highly substantial decrease in HbA_1C to 7.48, 6.58, and 7.14 respectively. However, there was a substantial decrease in HbA_1C to 6.84 in the group treated with Insulin and *C. longa* supplement. This indicates that the addition of *C. longa* supplement to hypoglycemic drugs produced a very valuable effect on glycemic control.

Effect on advanced glycation end products

Results presented in table 2 reveal that the curcumin supplement along with standard anti-diabetic glimepiride + metformin and glimepiride showed a highly significant decrease in advanced glycation end product CML as compared to the control group. While the sitagliptin + Metformin, the treatment group also revealed a significant decrease in the advanced glycation end product as compared to the control.

Table 2 compares advanced glycation end products in the treatment and control groups. The advanced glycation end products in groups treated with sitagliptin + metformin + curcumin showed a significant decrease on day 120 i.e. 515.55±18.41ng/ml. There was a highly significant decrease in advance glycation end products in the groups treated with glimepiride + metformin + curcumin and glimepiride + curcumin with the mean decrease to 464.61±15.47ng/ml and 485.55±12.45ng/ml respectively on day 120. This indicates that the addition of *C. longa* supplement to the standard therapy reduced the formation of advanced glycation end-product providing therapeutic benefit to the patients.

Neuropathic sensation by monofilament

It has been observed that neuropathic sensation was greatly improved in patients who were taking *C. longa* supplement along with different anti-diabetic medicine, importantly highly significant improvement was observed in patients who were taking *C. longa* along with either glimepiride plus metformin or glimepiride alone. It was also revealed that the persons who were in the control group showed a non-significant decrease in sensation in all groups except glimepiride control which showed a significant reduction in neuropathic sensation.

Table 3 shows the mean and SEM of all groups of control and treated patients with highly significant improvement in neuropathic sensation i.e. 9.20±0.17 and 9.47± 0.15 in groups treated with glimepiride + metformin +curcumin and glimepiride + curcumin respectively.

DISCUSSION

The objective of the study was to notice the effect of the *C. longa* supplement on the HbA1c, neuropathic sensation, and advanced glycation end-product level following its administration for 120 days. Results of the present study reveal that the curcumin supplement along with standard anti-diabetic treatment showed highly significant improvement (<0.001) in HbA1c of diabetic patients, particularly in patients taking sitagliptin + Metformin + curcumin, glimepiride + metformin + curcumin, and glimepiride + curcumin as compared to control groups. However, the insulin + curcumin group also revealed a significant decrease in HbA1c. The decrease in HbA1C in the present study is by Yuan *et al.,* (2022).

Similar effects on glycemia were also reported in animals and clinical studies which demonstrate that *C. longa* can reduce the blood glucose level in diabetes (Chougala *et al.,* 2012; Chuengsamarn *et al.,* 2012). Previously it was also reported that oral use of Curcuma can reduce body weight, decrease glucose and HbA1C in the blood, and also improve insulin sensitivity in the pre-diabetic population.

Table 1: HbA1C of Control and Treatment groups

Groups	HbA1C (%)		
	Day 0	After 60 Days	After 120 Days
Sitagliptin +Metformin (8)	10.98 ± 1.17	10.32±0.93	9.68±0.62
Sitagliptin +Metformin+ Curcumin (8)	11.99 ± 0.93	9.81±0.60	7.48±0.19**
Glimepiride +Metformin (15)	9.66 ±. 067	9.30±0.45	9.00±0.29
Glimepiride+ Metformin + Curcumin (15)	10.04 ± 0.46	8.31±0.21*	6.58±0.12**
Glimepiride (17)	9.65 ± 0.58	9.34±0.42	9.10±0.27
Glimepiride + Curcumin (17)	10.37 ± 0.45	8.85±0.24	7.14±0.12**
Insulin (5)	8.90 ± 0.60	8.73±0.46	8.83±0.15
Insulin +Curcumin (5)	9.16 ± 0.44	8.04±0.30	6.84±0.09*

Table 2: CML of Control and treated diabetic patient

Groups	CML (ng/ml)		
	Control Day 0	Treatment After 60 Days	Treatment After 120 Days
Sitagliptin +Metformin (8)	590.43±19.19	590.45±18.79	582.78±22.16
Sitagliptin +Metformin + Curcumin (8)	612.45±20.83	564.79±19.77	515.55±18.41*
Glimepiride +Metformin (15)	573.17±20.46	584.46±19.28	589.64± 19.27
Glimepiride +Metformin + Curcumin (15)	605.86±17.84	549.19±15.36	464.61±15.47**
Glimepiride (17)	544.08±13.01	542.53±7.46	536.13±3.74
Glimepiride + Curcumin (17)	618.09±16.06	558.85±14.71	485.55±12.45**
Insulin (5)	647.18±22.49	652.92±12.68	644.22±16.69
Insulin + Curcumin (5)	640.38±30.14	589.82±26.35	519.74±19.44

Table 3: Neuropathic sensation by monofilament

Groups	Neuropathic Sensations		
	Control Day 0	Treatment After 60 Days	Treatment After 120 Days
Sitagliptin +Metformin (8)	9.38±0.18	8.88±0.48	8.63±0.53
Sitagliptin +Metformin + Curcumin (8)	8.50±0.38	8.88±0.29	9.63±0.18
Glimepiride +Metformin (15)	9.20±0.24	8.93±0.28	8.67±0.19
Glimepiride +Metformin + Curcumin (15)	7.40±0.32	8.20±0.28	9.20±0.17**
Glimepiride (17)	9.41±0.15	8.94±0.23	8.41±0.28*
Glimepiride + Curcumin (17)	7.82±0.39	8.35±0.27	9.47±0.15**
Insulin (5)	9.60±0.24	9.00±0.32	8.40±0.40
Insulin+ Curcumin (5)	8.40±0.24	8.60±0.24	9.60±0.24

n= 90
*p less than 0.05 noteworthy
**p less than 0.01 highly substantial

Curcuma taken in diet also prompted beneficial effects on an increased level of fasting blood glucose, urine sugar, and urine volume in streptozotocin associated diabetic rats (Chougala *et al.,* 2012; Chuengsamarn *et al.,* 2012) whereas according to another study the daily intake of 1500 mg curcumin did not significantly reduce HbA_1C (Hodaei *et al.,* 2019).

In the current study, the effect of curcumin was studied on neuropathy with the help of microfilament sensation. It was noticed that the addition of curcumin supplement revealed highly significant improvement in neuropathic sensation in diabetic patients more importantly in groups taking glimepiride + Metformin + curcumin and glimepiride + curcumin. Similar effects were also observed in the animals which conclude that *C. longa* is actively involved in reducing diabetic neuropathy and effectively suppresses the development of cataracts in streptozotocin-induced diabetic rats. These effects were caused by reversing changes in fluid and lipid peroxidation, decrease glutathione, protein carbonyl content, and activation of antioxidant enzymes. This normalized the reduction of hydrophobicity and changes in the crystalline structure of the lens, which results in damage to neuroprotective function in diabetics (Aldebasi *et al.,* 2013; Park *et al.,* 2021). Another study in rats with streptozotocin-induced diabetic neuropathy concluded that significant improvement in neuropathic pain was observed with cold, thermal, and mechanical stimuli after 4 weeks of consecutive use of curcumin (Park *et al*., 2021).

According to Fleenor *et al.,* (2015), old mice had higher arterial AGEs expression than young animals following dietary curcumin supplementation. Hence nutritional supplementation of curcumin completely normalized aorta arterial AGEs in old mice. Another study (Sajithlal et al., 1998**)** showed that curcumin following 8 weeks of oral administration prevented accelerated accumulation of AGE-collagen in diabetic rats. Diabetic rats had higher levels of AGEs associated to control animals. One more study (Yu *et al.,* 2012) studied the effects of curcumin on modulating diabetic cardiomyopathy in rats.

In this study, animals were treated orally with curcumin at a dose of 100 or 200 mg/ kg/ d for 16 weeks. Results of the present study are also in line with previous studies and reveal that curcumin supplements along with standard anti-diabetic drugs showed a highly significant decrease of advanced glycation end products in diabetic patients and importantly patients taking glimepiride + metformin and glimepiride + curcumin as compared to control groups. However, patients on sitagliptin + Metformin+ curcumin revealed a significant decrease in advance glycation end products.

Similar effects of curcumin were also observed in an animal study and concluded that the curcumin has reduced the AGEs level in the diabetic rat after a dose of 100-200mg/kg /day for 16 weeks (Sajithlal *et al.,* 1998). A study recently conducted (Zhang & Kitts, 2021) revealed that curcumin notably reduces the formation of advanced glycation end products responsible for various metabolic complications. Another human study that used curcumin with Boswellia serrata (BSE) gum resin in non-diabetic athletes concludes that the combination is responsible for a significant decrease in AGEs levels (Chilelli *et al.,* 2016).

CONCLUSION

The present study anticipates that the addition of *C. longa* capsule as a supplement was supportive in reducing the complications of type II diabetes when given along with standard anti-diabetic medicine. It may be concluded that the addition of *C. longa* improves glycemic control by decreasing glycated hemoglobin A_1C. It may also be concluded that the addition of *C. longa* as a supplement significantly improves neuropathic sensation and decreases the formation of advanced glycation end-product thus improving the diabetes-related complication. Hence the present study highlights that the natural supplement *C. longa* provides beneficial effects in the type II diabetes population.

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