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Glycemic Control and Hepatoprotective Effects of *Curcuma Longa* Supplementation in Patients with Type 2 Diabetes

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Abstract: This study aimed to determine the effect of *Cucurma longa* L supplementation on blood glucose and albumin levels and the hepatoprotective action 3 g *C. longa* divided in three doses during a 60-day treatment. The goal of this investigation, which is a prospective cohort study conducted in a tertiary care hospital, was to evaluate the effect and safety of *C. longa*, a natural supplement for the management of diabetes. Ninety subjects were divided into a treatment group and a control group, each consisting of 45 individuals. The control group was given an antidiabetic agent without *C. longa* supplementation, whereas the treatment group was given *C. longa* supplementation, along with a prescribed antidiabetic medication. Blood samples were collected by venous puncture to measure the random blood sugar, albumin, ALT, and AST levels before and 60 days after *C. longa* supplementation. The results were analyzed using SPSS version 20, and values were expressed as mean ± standard error. After the 60-day treatment, the random blood sugar level significantly decreased in the treatment group, which received glimepiride, metformin, and *C. longa* capsule, relative to that in the control group, which received glimepiride and metformin only (195.73 ± 16.34 mg/dl vs. 264.53 ± 19.69 mg/dl). No significant change in the albumin, ALT, and AST levels were observed between the groups, indicating that *C. longa* exerts no hepatotoxicity. It could be concluded that *C. longa* supplementation is safe and that it significantly reduces blood glucose levels in diabetic patients. This is the only study that evaluates the effect of *C. longa* supplementation on glycemic control in diabetic patients in Pakistan.

Keywords: type 2 diabetes, *Curcuma longa*, random blood sugar, albumin, aspartate aminotransferase, alanine transaminase.

补充姜黄对 2 型糖尿病患者的血糖控制和保肝作用

摘要：本研究旨在确定补充西葫芦对血糖和白蛋白水平的影响以及 3 克龙牙在 60 天治疗期间分为三个剂量的保肝作用。这项调查是在三级医院进行的一项前瞻性队列研究，其目的是评估龙牙（一种用于管理糖尿病的天然补充剂）的效果和安全性。90 名受试者被分为治疗组和对照组，每组由 45 人组成。对照组服用抗糖尿病药物，但不补充龙牙，而治疗组服用龙牙补充剂和处方抗糖尿病药物。通过静脉穿刺收集血液样本，以测量在补充长龙藻之前和之后 60 天的随机血糖、白蛋白、ALT 和 AST 水平。结果使用 SPSS 20 版进行分析，数值以平均值±标准误表示。治疗 60 天后，接受格列美脲+二甲双胍+龙牙胶囊的治疗组随机血糖水平显着低于仅接受格列美脲+二甲双胍治疗的对照组（195.73±16.34 毫克） /dl 与 264.53 ± 19.69 毫克/分升）。各组之间未观察到白蛋白、ALT 和 AST 水平的显着变化，表明龙牙没有肝毒性。可以得出结论，

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龙牙补充剂是安全的，并且可以显着降低糖尿病患者的血糖水平。这是唯一一项评估长叶草补充剂对巴基斯坦糖尿病患者血糖控制效果的研究。

关键词：2 型糖尿病、姜黄、随机血糖、白蛋白、天冬氨酸转氨酶、丙氨酸转氨酶。

1. Introduction

The International Diabetes Federation (IDF) Middle East and North Africa (MENA) Region consists of 21 countries and territories, including Pakistan. According to the IDF, 55 million people in the MENA region are diabetic, and this number will increase up to 108 million by 2045. In Pakistan, the prevalence of type 2 diabetes among adults is 17.8%, which is 148% higher than that previously reported [1]. Poor glycemic control in patients with type 2 diabetes remains a major problem and is a significant risk factor for the development of advanced glycation end products that are responsible for diabetes-associated complications [27].

The remaining medical challenge is the maintenance of normal blood glucose levels in diabetics. Therapies are primarily intended to increase insulin sensitivity, to maintain normal blood glucose levels, and to reduce oxidative stress. A number of therapeutic remedies that delay disease progression have also been evaluated. Moreover, it has been observed that a number of plant products utilized in the traditional management of diabetes possess hypoglycemic effects, along with antioxidant properties [2].

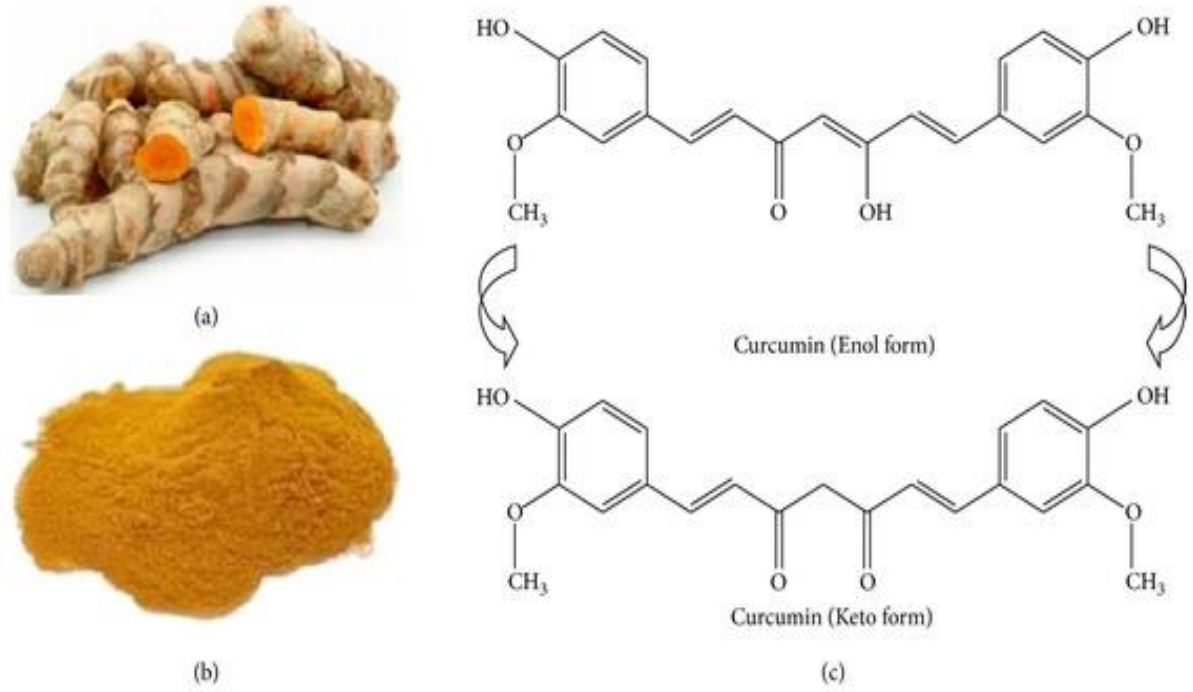

Fig. 1 Turmeric, curcumin, and its chemical structure: (a) The root of turmeric; (b) Powder of curcumin. Curcumin is the main active ingredient derived from the root of turmeric; (c) The enol and keto forms of curcumin are common structures of the drug [6]. Fig. 1(a) and 1(b) are from [25, 26]

In Southeast Asian countries, turmeric is commonly utilized as an additive that gives color and flavor and adds spice to food. In Ayurvedic, Siddha, and Unani medicine, *C. longa* is traditionally utilized as a home remedy to manage various diseases. The most active components of *C. longa* rhizomes are curcuminoids, including curcumin, bisdemethoxycurcumin, and demethoxycurcumin, which possess a wide range of biological activities, such as antioxidant, antiflammatory, and anticarcinogenic properties [3, 4, 5].

Most studies have examined the effects of *C. longa* using animal models [6, 7, 8, 9]. Only a few human studies exist, and the effects of *C. longa* in humans have not yet been established. Therefore, the present study evaluates the effects and safety of *C. longa* L in diabetes management.

2. Research Methodology

2.1. Study Plan

This work is a prospective cohort study conducted in a tertiary care hospital in Larkana. Patients were recruited from the Diabetic Outpatient Department of Shaheed Mohtarma Benazir Bhutto Medial University.

2.2. Inclusion Criteria

All participants were adults suffering from type 2 diabetes for not more than 10 years, aged 25–65 years, and with a body mass index (BMI) of 18.5–35 kg/m^2.

2.3. Exclusion Criteria

Type 1 diabetics, non-diabetics, patients suffering from hemoglobinopathy, patients with hepatic disease, and patients taking multivitamin and mineral supplements or taking herbal drugs during the last three months were excluded from this study.

2.4. *C. Longa* Capsule Preparation

Fresh *C. longa* rhizomes were washed with water to remove any adherent debris. The rhizomes were steamed for 10 min, cut into thin slices, oven-dried at 50°C for 8 h, and then finely ground using a high-speed blender. The powder was filled in 1 g capsules and then dispensed to patients to be taken three times a day.

2.5. Grouping and Consent

The 90 subjects meeting the inclusion criteria were divided into two groups: a control group, which received antidiabetic medicine without *C. longa* supplementation, and a treatment group, which received *C. longa* supplementation, along with the prescribed antidiabetic agents. On the basis of the antidiabetic medicine, the participants were further divided into sub-groups: 8 patients each from control and treatment groups were given sitagliptin and metformin, 17 patients from each group were given glimepiride, 20 patients were maintained on metformin and glimepiride, and 5 patients from each group received insulin.

A written informed consent was obtained from all the participants after being informed about the study objectives. The participants were informed not to change their lifestyle, dietary habits, physical activity, and anti-diabetic drug medication during the study period. This was ensured through counseling at the start of study and during each visit. The participants were also followed up on a weekly basis via telephone and were advised to report immediately to the investigator any adverse effect of the supplement. All the patients in the treatment group were directed to take 1 g *C. longa* capsule three times daily before each meal for 60 days, along with the prescribed antidiabetic drugs. After 60 days, the treatment group was compared with the control group, which was maintained on antidiabetic medicine without *C. longa* supplementation.

2.6. Sample Collection

The blood samples of all participants were collected *by a venous puncture* at the start of the study and after C. longa supplementation as per protocol. The ethylenediaminetetraacetic acid (EDTA) vials were used for blood sample collection. Tubes were centrifuged at 3000 rpm for 10 minutes to separate plasma. Biochemical parameters were measured in plasma using a Roche chemistry analyzer. Blood albumin concentration was measured by bromocresol green (BCG) method by transferring 20 ml of diluted standard, diluted sample, and blank to labeled tubes. A 1000 ml Roche diagnostics reagent was tapped lightly to mix. After mixing, it was incubated for minutes at room temperature. Then, the mixture was transferred to suitable cuvettes, and absorbance was measured at 620 nm [10]. Roche's reagent kits were used to estimate aspartate aminotransferase (AST) and alanine transaminase (ALT).

2.7. Statistical Computation

All the results were analyzed by using SPSS 20 version software. The values were expressed as a mean and standard error to the mean. One-way analysis of variance (ANOVA) was followed by the LSD for comparing the significance of biochemical parameters. The value difference of less than 0.05 was considered significant, and the values less than 0.01 were considered highly significant.

2.8. Ethical Approval

The current study was approved by the Ethical Review Committee of the Ziauddin University (Reference Code 3031220WAPHA, March 9, 2021).

3. Results and Discussion

Among 90 subjects who were part of the study, eight patients each from the control and treated groups received sitagliptin and metformin in combination, 17 patients each from the control and treated groups received glimepiride and metformin in combination, 15 patients each from the control and treated groups were maintained on glimepiride alone. Five patients each from the treated and control groups received insulin.

Table 1 reveals the RBS levels of control and treatment groups. The random blood sugar levels in groups treated with glimepiride and metformin at days 0 and 60 were 237.13 ±23.87 mg/dl and 264.53 ± 19.69 mg/dl, respectively. However, there was a highly significant decrease in random blood sugar to 195.73 ± 16.34 mg/dl of the group treated with glimepiride and metformin and

with C. longa supplement after 60 days. This shows that the addition of C. longa given as a supplement to the standard therapy produces a very beneficial effect on RBS.

Table 1 Random blood sugar level of control and treated diabetic patients

Groups	RBS (mg/dl)	
	Control Day 0	Treatment After 60 Days
Sitagliptin + Metformin Control (8)	172.25 ± 23.64	239.25 ± 48.9
Sitagliptin + Metformin Treatment (8)	252.00 ± 50.70	170.13 ± 21.75
Glimepiride + Metformin Control (17)	237.13 ± 23.87	264.53 ± 19.69
Glimepiride + Metformin Treatment (17)	313.07 ± 25.21	195.73 ± 16.34**
Glimepiride Control (15)	193.59 ± 16.48	256.47 ± 22.99*
Glimepiride Treatment (15)	285.65 ± 24.78	181.06 ± 14.60**
Insulin Control (5)	204.00 ± 7.12	239.20 ± 6.09
Insulin Treatment (5)	237.60 ± 10.21	162.20 ± 14.20*

N = 90
*p values less than 0.05 significant
**p values less than 0.01 highly significant

A similar effect was also observed when C. longa supplement was given in combination with standard antidiabetic agent glimepiride alone. The result was a highly significant reduction in RBS to 181.06 ± 14.60 mg/dl after 60 days as compared to the RBS in the control group (i.e., 256.47 ± 22.99 mg/dl). The beneficial effect of C. longa supplement was also observed when it was given in combination with insulin, and RBS levels were reduced to 162.20 ± 14.20 mg/dl after 60 days.

Table 2 reveals the effect of standard antidiabetic therapy on hepatic parameters when given alone as well as in combination with C. longa supplement. None of the group showed any significant change in hepatic parameters (i.e., ALT, AST, and albumin). This shows that C. longa supplement did not produce any toxic effect on the liver up to 60 days.

Table 2 ALT, AST, and albumin level in treatment groups with C. longa

Treatment Groups	Parameters		
	ALT (U/L)	AST(U/L)	Albumin (g/dL)
Sitagliptin + Metformin Day 0	26.50 ± 3.27	26.00 ± 2.14	4.46 ± 0.11
Sitagliptin + Metformin Day 60	23.88 ± 2.65	21.88 ± 1.65	4.65 ± 0.11
Glimepiride + Metformin Day 0	22.13 ± 1.92	20.20 ± 1.62	4.48 ± 0.07
Glimepiride + Metformin Day 60	19.20 ± 1.45	18.07 ± 1.19	4.59 ± 0.05
Glimepiride Day 0	24.76 ± 2.70	21.53 ± 1.78	4.61 ± 0.08
Glimepiride Day 60	23.29 ± 2.18	20.76 ± 1.92	4.56 ± 0.07
Insulin with Curcumin Day 0	23.60 ± 4.41	24.80 ± 2.92	4.68 ± 0.06
Insulin with Curcumin Day 60	26.20 ± 4.06	27.40 ± 3.17	4.59 ± 0.09

The aim of the study was to observe the effect of C. longa supplement on the blood sugar level, and its hepatoprotective effects following its administration for 60 days. Results reveal that the *C. longa* supplement capsule is responsible for a highly significant (< 0.001) decrease in blood sugar as compared to the control group (Table 1).

Though several studies have been conducted on *C. longa* and its derivative consumption on various body measurement indices and oxidative stress [11–18], only a few of these have been carried out on humans. Most of them have been performed on animal models for assessing the impact of curcumin on diabetes. The current study is the first one to be conducted in Pakistan to evaluate the effect of *C. longa* as a supplement for blood glucose levels among the diabetic population. One such study showed a significant decrease in fasting blood glucose levels with a 300 mg of curcumin supplement for three months [19], and another study showed no significant effect on fasting blood glucose levels [11]. However, the current study demonstrates a highly significant effect on blood glucose levels in diabetic patients with a daily dose of 3 g administered in three divided doses, as compared to the control group. This reduction in blood glucose levels may be due to the beta-pancreatic cells not being destroyed, resulting in improved beta-cell function and reduction in insulin resistance [20, 21]. According to one study that tested the anti-hyperglycemic effects of curcumin in rats with 80 mg/kg oral administration of curcumin and 1 mg/kg of rosiglitazone and a combination of both in treated groups and vehicles in the control group, the conclusion was that curcumin was responsible for improving the insulin sensitivity and anti-hyperglycemic effects, which may be due to its anti-inflammatory

properties [22]. The same anti-hyperglycemic effect is observed in the current study, particularly in diabetic patients who are taking insulin secretogouge medicine, which may be due to the improvement of insulin sensitivity by *C. longa*.

The current study demonstrates no significant change in albumin, AST, and ALT levels in patients treated with the curcumin capsule after two months of therapy. This study shows that the use of 3 grams of C. longa did not produce any adverse effects on the hepatic profile and indicates that a daily intake of 3 grams of C. longa is safe for the diabetic population to use to improve their glycemic control.

One study observed the effect of C. longa and ursodexycholic acid on rats with non-alcoholic fatty liver disease and concluded that C. longa and ursodexycholic acid usage improves liver function and causes a significant decrease in the AST and ALT liver enzyme level [23]. Another study concluded that in two cases taking a dose of curcumin (specifically 375mg of curcuminoids and 4 mg of black pepper per tablet) caused hepatitis and increased the AST and ALT level [24]. In this study, it has been observed that even a daily dose of 3 grams divided into three doses did not significantly affect the level of the AST and ALT liver enzyme. This indicates that curcumin does not compromise liver function contrary to what the above study, which is only based on two reported cases, concludes.

4. Conclusion

Diabetes mellitus (DM) is defined as a metabolic dysfunction that is identified by hyperglycemia and hyperuricemia and is related to a reduction of insulin production and defective β-cells function. Diabetes is one of the earliest global diseases. In 2017, the International Federation reported that 451 million people suffered from DM around the world, whereas the World Health Organization (WHO) revealed that the total estimate for DM was 19% of the world's entire population. DM creates a lot of problems in diabetic patients' lives and also decreases the patients' quality of life due to the high rate of mortality, morbidity, and expensive treatment. DM is commonly found in developing countries while it is estimated that more than 50% of diabetes cases are undiagnosed.

It has been observed by recent studies that C. longa possesses an important role in diabetes, but there are complications as a number of studies were conducted on animals to check the antidiabetic role of C. longa. However, a small number of studies were conducted on people to evaluate the effect of C. longa, most of them with an additive like piperine. Therefore, the novelty of the current study is that it is the only study conducted on the people of Pakistan to evaluate the effect of C. longa in diabetes as a single agent. Results of this study shows the C. longa supplement capsule to be effective in lowering blood glucose levels without any hepatic toxicity in the diabetic population. This natural supplement will lower the total cost related to diabetes by improving glycemic control without any adverse effects.

The limitation of this study is the small number of people evaluated. Before reaching a final conclusion, the C. longa supplement has to be tested on a larger number of patients for longer periods of time. Future prospects are to check the mechanism of the antidiabetic effect of C. longa and its effects on the HbA1c level.

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