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Original Research Article

A clinical study on *Clitoria ternatea* tea therapy to manage diabetic distress in people with type 2 diabetes

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Abstract

Objective: The purpose of this study was to assess the impact of supplementing with shankhpushpi tea or *Clitoria ternatea* flower extract (CTE) on changes in serum protein carbonyls and urine 5-Hydroxyindoleacetic acid (5-HIAA) levels in those experiencing diabetic distress.

Materials and Methods: A comparative study conducted with 30 healthy voluntaries as control group- CON, 90 type-2 diabetic patients experiencing moderate distress (as determined by a DDS-17 score between 2 and 3), 30 patients were assigned to either the DIAB, CTE-1 or CTE-2, with the CTE-1 group receiving 5 daily for 12 weeks and the CTE-2 group receiving 10 daily. Serum protein carbonyls and urinary 5-HIAA levels were assessed at the end of the twelfth week to conclude the preventive role of CTE on diabetic distress in the type-2 diabetic population.

Results: Out of the 114 individuals initially enrolled in the study, 90 were included in the final analysis. The diabetic distress group (DIAB) exhibited significantly elevated levels of protein carbonyls and significantly decreased levels of 5-HIAA ($p<0.001$). In comparison to the CON group, the administration of both Shankhpushpi 5 g and 10 g extracts resulted in a significant reduction in serum protein carbonyls and an increase in urinary 5-HIAA, demonstrating a statistically significant compared with control ($p<0.001$).

Conclusion: Shankhpushpi tea supplementation is beneficial in improvement of diabetic distress (quality of life) in diabetic patients.

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Introduction

Diabetes is a metabolic disease whose patients often have co-occurring mental health conditions such as anxiety and depression in addition to other medical conditions (Balhara 2011). Type-2 diabetes with early onset is associated with an exceptionally high frequency of psychosocial disorders. It has been demonstrated that 10% to 30% of diabetics suffer from subthreshold depression or serious depressive disorder, and it covers both diagnosable mental diseases and problems specific to living with diabetes (Lee et al. 2023). Conversely, diabetes depression can cause a persistent feeling of hopelessness, disinterest, low self-esteem, tiredness, and other emotional problems (Darwish et al. 2018). "Diabetes distress" is the term used to describe the uncomfortable feelings and weight of self-care that come with having diabetes. This phrase is used to express the depressing and upsetting feelings that accompany having diabetes, particularly the requirement for ongoing care and monitoring, the ongoing concern about complications, and the potential for relationships in both the personal and professional spheres to fail (Abuhegazy et al. 2022). Diabetes distress and depression are not the same thing; although they both exist concurrently and independently, diabetes distress is characterized by emotional problems affecting patients' mental health and quality of life (Owens-Gary et al. 2019). The severity of diabetic distress is directly correlated with the complexity and duration of the condition (Inverso et al. 2022). According to recent studies, the proportion of young diabetics in India who experience diabetes distress has climbed to about 37.97% (Ranjan et al. 2023).

Therefore, it is crucial to address and manage psychological distress in individuals with diabetes in order to maintain proper glycemic control. Medication and psychotherapy are essential components of conventional depression treatment. Side effects of antidepressant medication can include increased weight gain, increased insulin resistance, and potential cardiotoxicity. Psychotherapy may not be suitable for treating diabetic patients, as noted by (Pfaltz et al. 2017). Archived discoveries propose that upsetting experience is one of the significant guilty parties in the beginning and backslide of clinical depression (Olufunmilayo et al. 2023). Complementary and alternative therapies for diabetes, such as acupuncture, yoga, hydrotherapy, and nutritional supplements, are less likely to cause harm compared to conventional methods. According to a study by Alqathama et al. in 2020 (Alqathama et al. 2020), herbal supplements have shown more promising results in managing diabetes than other alternative therapies. Oxidative stress is brought on by overeating and sedentary lifestyles which are the main factors contributing to the onset of metabolic syndromes and other complications of diabetes (Bhatti et al. 2022). Because oxidative stress has high oxygen consumption and a lipid-rich composition, it plays a role in cerebral biochemical impairment (Jeyaraj et al. 2021). Consequently, there is a good chance that brain damage brought on by oxidative stress will have a detrimental effect on regular Central Nervous System functions. While oxidative harm has frequently been linked to neuropsychiatric disorders such as depression and anxiety disorders, as well as neurodegenerative disorders, awareness of this link is growing. The quality of life is affected by both neuropsychiatric and neurodegenerative disorders (Bailo et al. 2022). Patients with diabetes also encounter alterations in their quality of life, which is linked to better glycemic control.

Protein carbonylation, or protein oxidation, can be induced by reactive oxygen species (ROS). Usually, it refers to a process that yields reactive aldehydes or ketones that have the ability to damage any kind of biomolecule. Carbonylated proteins undergo more structural and functional

changes; they induce accumulation and cytotoxic effects and susceptibility to apoptotic triggers. As investigated in preclinical models of carbonyl protein - associated illnesses like diabetes, have demonstrated that modulating the synthesis of carbonylated proteins offers a potentially effective alternative strategy to traditional approaches that concentrate on oxidative stress. Multiple protein malfunctions by carbonyl proteins are quite dangerous because they can upset the redox equilibrium in cells and have an impact on the cell cycle, which can lead to the death of neurons.

The behavioral, emotional, and depressive aspects of diabetic distress are associated with synapse changes in both quantity and quality, and these progressions are mirrored in the clinical indicators of diabetic distress (Thakur et al. 2019). The structure and functions of synaptic proteins, which are crucial for synaptic integration and neuronal function, can be altered by protein carboxylation (Xiejun et al. 2018). Nervous system chemicals such as serotonin, also known as 5-hydroxytryptamine (5-HT), control behavior, mood, memory, and stomach homeostasis, among other physiological functions. Expanded serotonin (5-HT) turnover has been associated in various human and animal review to primary, behavioral, and biochemical changes in the focal sensory system in diabetic patients as well as a large group of different changes saw in rat models of diabetes (Thakur et al. 2019). Insulin-related impairment According to Spiegelaar et al. in 2023, it has an impact on the metabolism of tryptophan and serotonin (Spiegelaar et al. 2023). It also modifies the amount of serotonin and the metabolic end product 5-Hydroxy Indole Acetic Acid (5-HIAA). Patient with depression shows a huge decrease in the degrees of 5-HIAA. 5-HIAA, a measure of serotonin levels, is used to estimate the amount of serotonin in the cerebrum. The fast debasement of serotonin to 5-HIAA has prompted evidence supporting 5-HIAA's role as a depression biomarker (Jayamohananan et al. 2019).

Clitoria ternatea, also known as butterfly pea, is a long-lasting herbaceous plant in the Fabaceae family. It is commonly cultivated in temperate and tropical climates worldwide. In South India, it is referred to by the traditional name 'shankhpushpi'. *Clitoria ternatea*, viewed as a nootropic spice in Ayurvedic medication, has gathered a great deal of consideration recently due to its likely purposes in contemporary medication as well as it is recognized for its natural food coloring properties and its ability to combat free radicals. According to several animal studies, the extracts of C. ternatea have anti-inflammatory, pain-relieving, diuretic, nootropic, anti-asthmatic, calming, antipyretic, cellular energy stabilizing, anti-arthritic, antioxidant, and wound-healing properties (Mukherjee et al. 2018). The findings from the in vitro and animal testing of C. ternatea CT extracts suggest that they may consist of multiple constituents working together (Rajamanickam et al. 2015).

A later investigation of the impacts of shankhpushpi withdraws diabetic-prompted cognitive loss tracked down a critical lessening in acetylcholinesterase movement, oxidative pressure, and significant expansions in cell free radical fighting capacity (Svedbo Engström e al. 2019). According to another current analysis, autophagy in the brain of mice treated with CT for 60 days significantly decreased (Bhatti et al. 2022). In Shankhpushpi, the majority of studies focused on secondary metabolites, primarily water-soluble Flavonoids like anthocyanins, flavonols like quercetin, and glycosylated Flavonoids, which are thought to be in charge of nature's positive effects (Jeyaraj et al. 2021). There are variations of secondary metabolite in shankhpushpi, which have all great characteristics to oversee diabetic distress. In this manner, it is important to show the impact of CT in the administration of diabetic distress.

However, there is a lack of research on the relationship between oxidative stress and quality of life. Oxidative stress is the primary pathophysiological mechanism for the development of all microvascular and macrovascular complications in diabetes (Bhatti et al. 2022), and it can damage the nervous system. Because of this, our study focused on managing oxidative stress in conjunction with glycemic control using traditional herbal treatments, which yielded better results in terms of quality of life than good glycemic control through conventional pharmacotherapy. The diabetic distress score (17 scale) was used to assess the quality of life of individuals suffering from type 2 diabetes.

Glycemic control is one of the goals of diabetes management that can be impacted by diabetic distress (Almomani & Al-Tawalbeh, 2022). Therefore, in the diabetic population, managing diabetic distress is more important than managing glycemic control. The consumption of tea is widespread across the globe. Herbal teas, in particular, are more popular as caffeine-free drinks. The blue tea beverage is made from CT is a distinctive color and a vibrant beverage. It is a wonderful addition to any diet because it is not only visually stunning but also has many health advantages (Mukherjee et al. 2018). This substance contains numerous flavonoids which are beneficial for cognitive function. It also contains antioxidants which are effective in eliminating free radicals, as noted by Rajamanickam et al. (Rajamanickam et al. 2015). Furthermore, its strong anti-inflammatory properties make it useful in addressing mild inflammatory conditions such as diabetes. Additionally, it exhibits anxiolytic properties, aiding in calming individuals and reducing anxiety, as indicated by Alpate et al. (Alpate et al. 2014). Finally, Aqueous extract of CT possesses anti-diabetic properties. Clitoria ternatea and other plants have the potential to treat diabetic distress due to their characteristics and chemical composition.

Urinary 5-HIAA, which shows alterations in serotonin levels in diabetic distress, and protein carbonyls, which are indicators of oxidative stress, were the two research subjects chosen. As far as the authors are aware, no previous clinical investigation has evaluated the impact of supplementing with shankhpushpi beverage on changes in urine 5-HIAA and protein carbonyls in individuals with diabetic distress. The primary goal of this study was to assess how supplementing with shankhpushpi beverages affects the diabetic distress score in individuals with type -2 diabetes mellitus.

Materials and Methods

Study population

Grown-up subjects matured 20-60 years were enrolled in the General Medication General Medicine outpatient department, Konaseema institute of medical sciences and research foundation (KIMS&RF). Diabetic subjects were concluded to have Type-2 diabetes Mellitus (T2DM) in light of the criteria established by the American Diabetes Association (Fasting blood Sugar-FBS greater than 126 mg/dl or a plasma glucose level greater than 200 mg/dl after two hours or hemoglobin A1C (HbA1C) > 6.5%) (Veríssimo et al. 2023) and accepting just metformin as their primary antidiabetic medication and control subject FBS < 100 mg/dl or hemoglobin A1C (HbA1C) > 6.0%. Prohibition models were viewed as participation in a corresponding preliminary, childbearing, hormonal imbalance other than adult-onset diabetes, inconceivability to give informed assent, presence of deadly diseases, constant hepatic and kidney disappointment (underwent hemodialysis or azotemia), history of psychological maladjustment or communication problems, for example, rheumatoid joint inflammation, and intense contamination of infected materials, high blood sugar due to non-diabetic, being allergic to the review medication(metformin), getting hormone treatment or

other herbal supplements, and unable to follow the study.

Study design

This was a comparative study conducted on T2DM patients from September 2022 to March 2023 at General Medicine outpatient department, Konaseema institute of medical sciences and research foundation (KIMS&RF) located in Konaseema district in Andhra Pradesh. After being evaluated for study eligibility, control and diabetic subjects were found to meet the inclusion criteria. As per study flowchart (Figure 1) a baseline measure of diabetic distress was assessed in eligible subjects using the Diabetes Distress Scale (DDS), which was invented by (Polonsky et al. 2005) the score of mean less than two denotes no distress, between two and three indicates moderate distress, and more than three denotes severe distress. After being chosen for the study, the healthy adult voluntaries included in control group CON, study the subjects with moderate diabetic distress were split up into three groups: Patients in diabetic control group II (DIAB) had metformin-only treatment. Five gram CT flower extract supplements were given to diabetic distress patients with metformin in CTE-1 Group III, and 10 gram CT flower extract supplements were given to diabetic distress patients with metformin in CTE-2 Group IV for a 12-week period after breakfast and after dinner two times per day. Patient care personnel received training on drug administration from qualified staff members

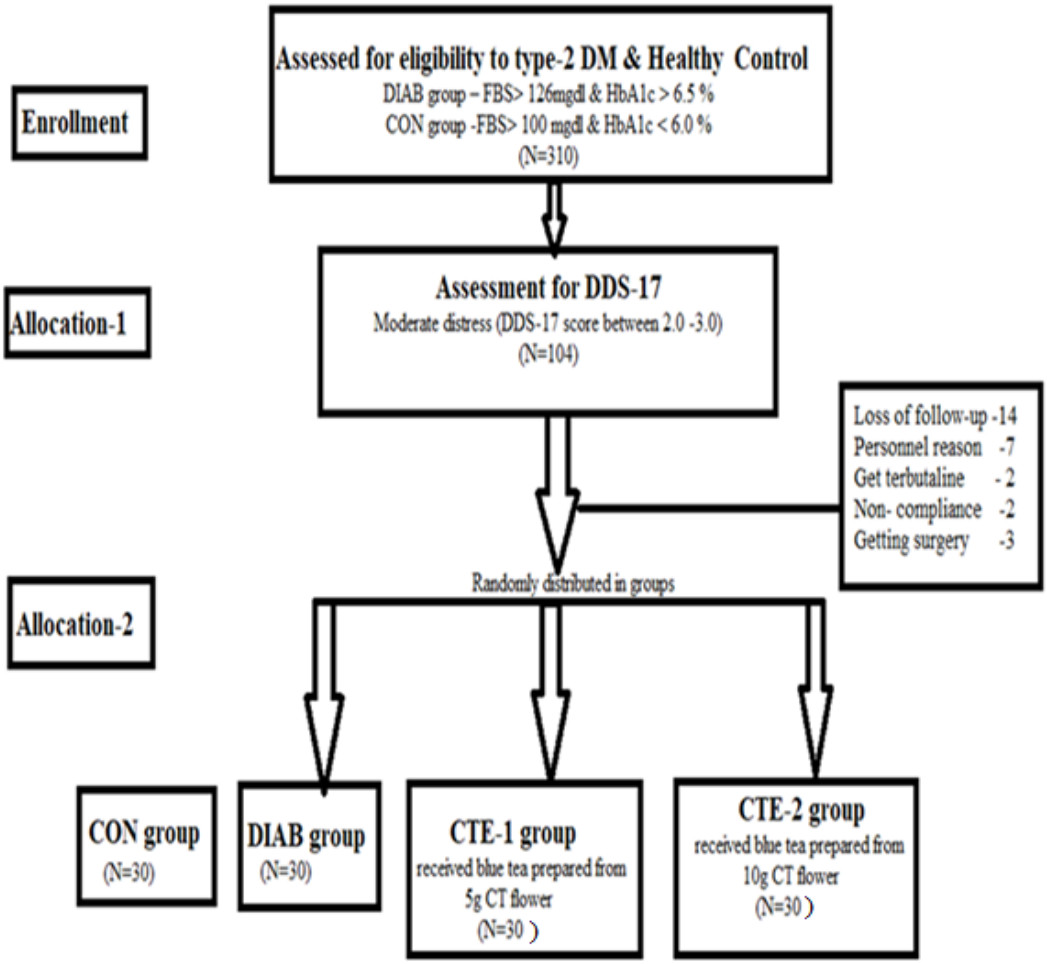

Figure 1. Study flow chart

Ethics

According to Indian Council of Medical Research rules (Ref No. 61/MMCH&RI/2021), the protocol was authorized by the Institution Committee of Ethics in Human Research, which is part of Meenakshi Medical College Hospital & Research Institute. After being informed, every patient signed a written informed permission form to take part in the research.

Sample size

The current study's sample size was established using the formula below to compare the two independent groups' means. With a type one error rate of 5%, 50 samples are obtained assuming A comparable quantity of patients within each category ($\varphi = 1$), Statistical accuracy of 80% for recognizing a standard effect size ($\Delta = 0.8$) (6) for the primary outcomes of the study. We took into account an extra 20% of the sample to account for potential attrition by Nasab et al (Nasab et al. 2023) study included 104 diabetic distress patients to assign patients at random to receive either the metformin treatment (n=30) or the metformin with butterfly pea supplement (CTE-I) (n=30) or the Metformin with butterfly pea supplement (CTE-II) (n=30) for a 12-week period. Due to staff issues, three surgeries, two non-compliance cases, asthma therapy, and seven diabetic distress patients, follow-up was missed on fourteen of them.

Plant preparation and extraction

Butterfly pea, or *Clitoria ternatea L.*, is a widely grown plant in southern India. Nearly all of the homes in the area have gardens or hedges that are home to this perennial vine. In tropical areas, Shankhpushpi, a language from south India, is widely spoken. In the east Gothwari district of Konaseema, it is a common garden flower used for both drinking and god-worshipping. In the department of spices, plantations, medicinal, and aromatic crops at Dr. Y.S.R. Horticulture University, Venkataramannagudem, West Godavari District, Andhra Pradesh, India, the flower of CT was recognized and turned into a herbarium voucher (Voucher Number: 78/2021). An aqueous extract (herbal tea) was made from 5 and 10 g of CT flowers in 150 ml of drinking water. Reduced to 100 ml by boiling it for 10 min.

Study procedure

This study was planned as a comparative study consisting of four groups. Group I (control) thirty healthy control; Group II diabetic subjects received only metformin: Group III diabetic distress subjects received metformin and butterfly pea supplement (CTE-1); Group IV diabetic distress subjects received metformin and butterfly pea supplement (CTE-2). Based on participation criteria, diabetic distressed patients were divided into the DIAB group, CTE-1 group, and CTE-2 group for supplementation with CT flower extraction for 12 weeks.

Patients were told not to eat bananas, kiwis, pineapple, walnuts, eggplant, or fruits in general until the study was over. Patient instructed to collect 24 hr urine, urine collection in dark color container with 10-15 ml glacial acetic acid as a preservative. Samples of fasting blood are taken at the conclusion of the 12-week period; the patient is given a diabetic distress score. DDS-17 was used to determine the degree of distress in diabetes. separates the four primary subscales from the main term that reflect various possible areas of diabetes-specific distress: 5 items in emotional burden (EB), 4 items in physician-related distress (PRD), 5 items in regimen-related distress (RRD), and 3 items in interpersonal distress (ID). A mean DDS-17 score of less than two denotes no distress, between two and three indicates moderate distress, and more than three denotes severe distress.

Measurement of Urine HIAA

The amount of 5-HIAA was determined by a mass spectrometric method

(Jayamohananan et al. 2019) and 5-HIAA measurements expressed as mg/day.

Assay for protein carbonyls

Protein carbonyls were measured by spectrophotometry using Brady's reagent, a hydrazine derivative, following the protocol described by Reznick and Packer and results were expressed as nanomoles of the carbonyl group per milligram of protein.

Statistical analysis

Descriptive statistics were accessed and results are expressed as an arithmetic mean ± standard error. Statistical significance between the control and experimental group was assessed by using statistical procedure one-way ANOVA, followed by the Tukey-Kramer multiple comparison tests. $p<0.05$ was considered significant.

Results

To assess the anti-stress capability of CT extract against diabetic distress, 30 healthy non-diabetic individuals were chosen from among 90 diabetic distress patients (moderate discomfort; DDS-17 score 2-3). Ten participants withdrew from the research because of reasons that were not associated with the research (Figure.1); remaining ninety participants were carried out study their clinical and demographic characteristics are presented in Table 1. The liver marker enzyme and kidney marker tests did not reveal any adverse events following the consumption of butterfly pea beverages.

Clitoria ternatea extract attenuates Diabetic distress in type-2 diabetic patients

We discovered a substantial average distinction between the diabetic and control group ($p<0.001$) in the diabetic distress scores on the DDS-17, demonstrating how diabetes complications affecting the nervous system in diabetic group have noticeably worse quality of life symptoms. Significant mean differences were discovered, according to the results. based on the DDS-17 score, which shows sub scale emotional burden 70%, physician burden 69%, regimen distress 73%, interpersonal distress 66% and overall diabetes distress 47% reduction in the experimental group's level of distress (Figure.1 and Table.2), health, emotional distress, and depression when compared to the CTE treated groups and the diabetic group. Finds shows there is no significant difference between CTE-1 and CTE-2 group, it shows that optimum distress activity at 5 gram of butterfly pea.

Table1. Illustration of demographic characteristics in control and diabetic experimental subjects.

Total patient	Control	Diabetic	CTE-1	CTE-2
Age (years)	31.44±6.78	37.9±4.76	40.37±5.73	338.1±4.76
Male	60%	73%	73%	63%
Female	40%	26%	26%	40%
FBS (mg/dl)	91.66±10.3	252.97±62.2^{a**}	205.5±59.36^{b*}	190.26±67.46^{b*}
HbA1c (%)	5.38±0.25	7.86±0.73^{a**}	7.23±0.67^{b*}	7.12±0.54^{b*}
Hypertension (%)	-	56%	50%	53%
ALT (IU/L)	25.97±5.22	31.87±6.96	29.26±6.68	28.03±6.71
AST (IU/L)	23.10±4.00	26.76±4.97	23.97±4.28	24.27±4.31
ALP (IU/L)	136.76±26.61	128.47±29.7	119.57±23.73	128.46±29.69
Creatinine (mg/dl)	0.96±0.26	1.64±0.32	1.33±0.36	1.24±0.34
Urea (mg/dl)	25.55±6.27	29.05±5.28	21.93±7.5	20.16±6.32

In the Table, the results represent the arithmetic mean with ± predictable error of thirty experimental subjects. The statistical drift of the study was set at p value less than 0.05* or p value less than 0.01**. ANOVA between the experimental groups was performed and mentioned in the bar diagram as a symbol of a-compared with the control group mean; and b-compared with the mean of diabetic group.

Table2. Illustration of diabetic distress score 17 and subclasses of DDS-17 in control and diabetic experimental subjects.

DDS-17 score	Control	Diabetic	CTE-1	CTE-2
EB	1.28±0.19	2.67±0.22	1.62±0.20	1.6±0.18
PRD	1.34±0.31	2.75±0.09	1.69±0.14	2.2±0.11
RRD	1.31±0.32	2.82±0.07	1.74±0.11	1.7±0.11
ID	1.32±0.30	2.42±0.21	1.55±0.10	1.6±0.11
TOTAL DDS-17 score	1.31±0.23	2.7±0.077[a,**]	1.65±0.08[b,**]	1.8±0.07[b,**]

EB- emotional burden: PRD- physician-related distress: RRD- regimen-related distress: ID- interpersonal distress. In the table, the results represent the arithmetic mean with ± predictable error of thirty experimental subjects. The statistical drift of the study was set at p value less than 0.05* or p value less than 0.01**. ANOVA between the experimental groups was performed and mentioned in the bar diagram as a symbol of a-compared with the control group mean; and b-compared with the mean of diabetic group.

Effect of Shankhpushpi extract on urinary 5-HIAA

The serotonin metabolite level of the urine 5-HIAA showed a significant average difference ($p<0.001$) between the diabetic group and the control group, illustrating how emotional and behavioral changes brought on by diabetes complications are affected by changes in serotonin levels in the nervous system, which are indicative of a urinary 5-HIAA level in type 2 diabetic patients having noticeably worse quality-of-life symptoms. Treatment with butterfly pea flower extract (CTE) resulted in a 56% increase in urinary 5-HIAA levels, from 1.43 mg/day (2–9 mg/day) to 5.13 mg/day. This illustrates the relationship between serotonin levels and diabetic-mediated distress.

Clitoria ternatea extract's potential use in treating diabetes patients' protein oxidation

Findings revealed that, in comparison to healthy human subjects, diabetes mellitus patients had significantly higher serum protein carbonyl contents ($p<0.01$). Since an increase in carbonyl contents is a defining feature of protein oxidation, an increase in protein carbonylation is thought to be the most accurate biomarker of protein oxidation. The function of protein carbonylation in diabetic patients receiving butterfly pea flower extract has also been identified. According to our unique data, patients with diabetes treated with CTE had significantly lower protein carbonyl content than patients without diabetes ($p<0.01$).

Discussion

In the current study, 12-weeks of supplementation with Shankhpushpi beverage was effective in significantly improving blood glucose, diabetic distress score-17, oxidative stress marker and depression marker in type-2 diabetic patients. To our knowledge, this is the preliminary research study to have determined the effect of CT on diabetic distress and urinary 5-HIAA level in diabetic stressed subjects.

According to the results of the current investigation observed no negative effects on markers of renal or hepatic function. Similar finding was also seen in Chusak C et al study (Chusak et al. 2018). Furthermore, evaluation in our study shows significant decline in fasting blood glucose (FBG). Our reports in line with Khatib et al study (Khatib et al. 2024). reported a significant decline in fasting blood glucose (FBG). Further, the utilization of CT flower drink has been accounted for to assist control postprandial blood glucose in individuals affected by type 2 diabetes (Svedbo Engström et al. 2019). The investigation of the antidiabetic properties of the extract derived from the flower of CT was conducted in animal models, demonstrating its ability to effectively reduce blood glucose levels and liver marker enzyme

levels in streptozotocin (STZ) and nicotinamide-induced diabetic rats (Widowati et al. 2024). Furthermore, research has indicated that CT with gold nanoparticles exhibit promising antidiabetic and antioxidant properties, as demonstrated by Talpate et al. (Talpate et al. 2013).

According to our research, patients with diabetes have a significantly lower quality of life than subjects in good health ($p<0.05$) based on their score on the DDS-17. In line with the current study, Nanayakkara et al. reported a significant increase diabetic distress score -17. In addition, depression and diabetic stress were elevated in type 2 diabetes mellitus, as measured by the Beck's Depression Inventory (BDI-II) and the Diabetes Distress Scale (DDS) (Nanayakkara et al. 2016). Oxidative stress is brought on by overeating and sedentary lifestyles, which are the main factors contributing to the onset of metabolic syndromes and other complications of diabetes (Bhatti et al. 2022). Because oxidative stress has high oxygen consumption and a lipid-rich composition, it plays a role in cerebral biochemical impairment (Jeyaraj et al. 2021). Consequently, there is a good chance that brain damage brought on by oxidative stress will have a detrimental effect on regular CNS functions. While Oxidative harm has frequently been linked to neuropsychiatric disorders such as depression and anxiety disorders, as well as neurodegenerative disorders, awareness of this link is growing. The quality of life is affected by both neuropsychiatric and neurodegenerative disorders (Bailo et al. 2022). Patients with diabetes also encounter alterations in their quality of life, which is linked to better glycemic control. The findings of this study revealed the remarkable influence that CT flower beverage CTE supplementation had on the distress experienced by patients with type-2 diabetes. To our knowledge, this represents the inaugural exploratory inquiry into the impact of CT on diabetic distress. According to our research, patients with diabetes have a significantly improve quality of life by decreasing diabetic distress compare with subjects in good health ($p<0.05$) and CTE-2 (10 g CT flower used to extract beverage*)* were have better improvement compare to CTE-1 (Figure 2 and Table 2). Because the CTE flower extract contains dolphinidin anthocyanin, which has anxiolytic, anti-inflammatory, and antioxidant properties. Moreover, the plant *Clitoria ternatea*, has long been used in Ayurvedic medicine as a "tonic of the nerves", memory enhancer, nootropic, anti-stress, anxiolytic, antidepressant, and anticonvulsant agent. The focus is on CNS-related anti-inflammatory agents, according to the ethno pharmacological *Clitoria ternatea* evaluation of Asian Indian medicine use (Raghu et al. 2017). The pharmacology assessment in a prior study on the flower of CT indicated that it acted as an antidiabetic, prevented testicular damage, and was an anti-platelet and muscle relaxant agent (Coplan et al. 2014).

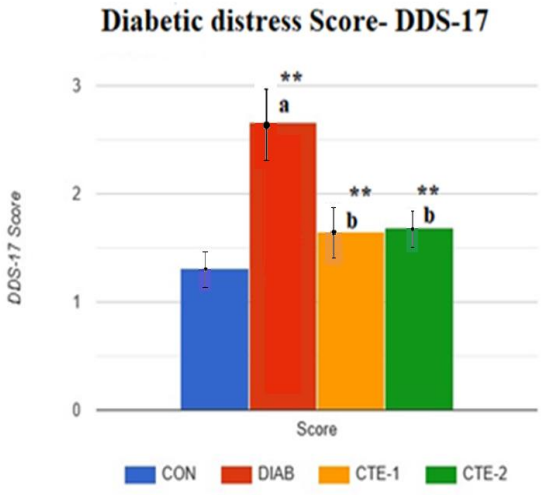

Figure 2. Illustration of diabetic distress score-17 in control and diabetic experimental subjects. In the bar diagram, the results represent the arithmetic mean with ± predictable error of thirty experimental subjects. The statistical drift of the study was set at p value less than 0.05* or p value less than 0.001**. ANOVA between the experimental groups was performed and mentioned in the bar diagram as a symbol of a-compared with the control group mean; and b-compared with the mean of diabetic group.

While serotonin metabolite 5-HIAA is a stable molecule found in both plasma and urine, it is an unstable neurotransmitter that has a stronger effect on the relationship between depression and diabetic distress (Prabhakar et al. 2015). Our research revealed that the 5-HIAA level (Figure.3), which was measured in diabetic patients, was considerably lower than in healthy subjects ($p<0.05$). This suggests that diabetic distress is linked to a serotonin deficiency in the nervous system, which will cause emotional and behavioural changes in diabetic subjects. When treated with shankhpushpi flower extract (CTE), the diabetic subjects' 5-HIAA level increased significantly ($p<0.05$) in comparison to the non-treated diabetic subjects (Figure.3).

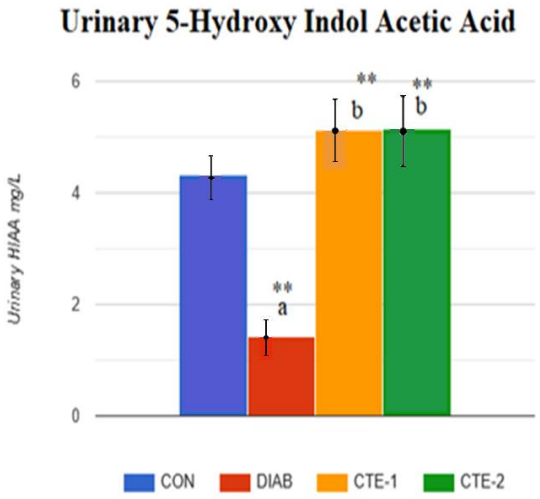

Figure 3. Illustration of urinary 5-HIAA level in control and diabetic experimental subjects. In the bar diagram, the results represent the arithmetic mean with ± predictable error of thirty experimental subjects. The statistical drift of the study was set at p value less than 0.05* or p value less than 0.001**. ANOVA between the experimental groups was performed and mentioned in the bar diagram as a symbol of a-compared with the control group mean; and b-compared with the mean of diabetic group.

Due to the anxiolytic effect of the anthocyanin in the shankhpushpi flower extract, this suggests that the serotonin levels in diabetic subjects have returned to normal. Recent studies have shown that the ethanolic extract of Shankhpushpi has a neuroprotective effect and can increase the concentration of serotonin in the brain tissue homogenates in propionic acid-induced behavior and memory impairment in autistic rats (Jili & Muralidharan 2021). Another in silico study shows that phytoconstituents from Shankhpushpi as potent MAO inhibitors prevent depression by increasing serotonin levels (Margret et al. 2015).

The current investigation revealed that protein carbonyls were greater in the DIAB group than in the CON group. These results suggested that inadequate glycemic control may be the cause of the oxidative stress seen in the DIAB group. Our findings are in agreement with those of (Almogbel et al. 2019) and (Song et al. 2020). ROS was responsible for the carbonylation of certain amino acid side chains by direct metal-catalysed oxidation. In addition, carbonyl groups can also be indirectly incorporated into proteins by the non-oxidative covalent addition of reactive carbonyl species. Chronic oxidative stress is associated with neuro-inflammation (Li et al. 2023); it is the mirror-image evidence of synaptic changes in diabetic distress as a clinical indicator of behavior, emotion and depression (Thakur et al. 2019). A notable reduction in serum protein carbonyl levels was observed in both CTE-1 and CTE-2 groups (Figure. 4). This study represents the first investigation to examine the impact of Clitoria ternatea on protein carbonyl levels in type 2 diabetes mellitus within a clinical setting. According to Chusak et al. the acute consumption of CTE resulted in an increase in plasma antioxidant capacity and a decrease in malondialdehyde (MDA) levels in participants who received 1 g and 2 g of CTE (Chusak et al. 2018). Additionally, the administration of 2 g of CTE increased postprandial plasma antioxidant status in the high-fat meal challenge in overweight and obese participants. Thus, these effects could also be reasons for the reduced protein carbonyls in diabetic patients who are under stress (Diabetic distress).

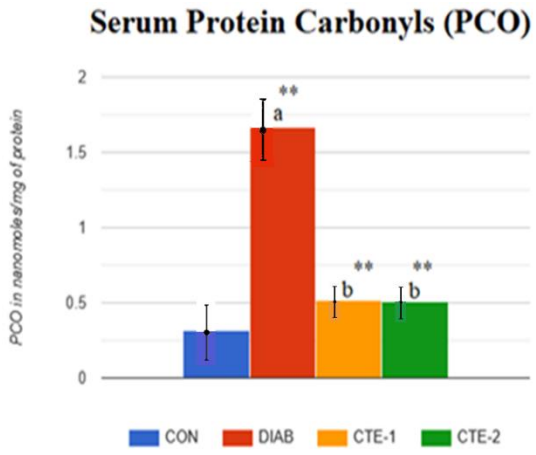

Figure 4. Illustration of serum protein carbonyl content level in control and diabetic experimental subjects. In the bar diagram, the results represent the arithmetic mean with ± predictable error of thirty experimental subjects. The statistical drift of the study was set at p value less than 0.05* or p value less than 0.001**. ANOVA between the experimental groups was performed and mentioned in the bar diagram as a symbol of a-compared with the control group mean; and b-compared with the mean of diabetic group.

The emotional and behavioral quality of life for people with diabetes is enhanced by the consumption of CTE beverages. Furthermore, serotonin content rises with CTE. simultaneously mitigating the oxidative damage of proteins in the diabetic population. One of the study's limitations was the lack of an assessment of the effect of CTE on other diabetes issues. Thus, more clinical studies should evaluate these effects as well as the underlying mechanisms. Further research in larger populations and multicenter studies involving a range of ages and ethnic backgrounds is recommended in order to further understand the therapeutic benefits of CTE for the management of diabetic issues. If these studies yield encouraging results, we will be able to advocate for public health policies that highlight the potential of using low-tech beverage-based interventions in the fight against diabetes.

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Conflicts of interest

The authors report no conflicts of interest.

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Ethical Considerations

The protocol was approved by the Institution Committee of Ethics in Human Research, which is a division of the Konaseema Institute of Medical Sciences & Research Foundation, in accordance with Indian Council of Medical Research regulations (Ref No. IEC/PR/2021:114). Each patient who wished to participate in the research signed a written informed permission form after being informed.

Authors' Contributions

V.M: Conceptualization, methodology, investigation, formal analysis, and drafting the manuscript; R.B: Formal analysis and writing-original draft; B.S and M.N: Visualization, and writing - review & editing; S.C: Visualization and writing - original draft; N.K: Writing-original draft and investigation; S.D.G and S.U: Investigation, Formal analysis, supervision, and project leadership. All authors have reviewed and endorsed the final manuscript.

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