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A CLINICAL TRIAL TO ASSESS THE ANTIDIABETIC, ANTIDYSLIPIDEMIC AND ANTIOXIDANT ACTIVITIES OF *TINOSPORA CORDIFOLIA* IN MANAGEMENT OF TYPE – 2 DIABETES MELLITUS

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Tinospora cordifolia-Hypolipidemic agent-Plant antioxidant-Oxygen free radical scavengers-Lipoprotein profile-LCAT.

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ABSTRACT: The present study was carried out to explore anti-diabetic, antidyslipoproteinemic and anti oxidant activities of *Tinospora cordifolia* (Menispermaceae) in type 2 diabetic patients. In this study clinical trial was conducted on type 2 diabetic patients attending the diabetes OPD, at Kaya Chikitsha Vibhag, Rajkiya Ayurvedic Chikitsha Mahavidyalaya, Touriya Ganj, Lucknow, following all ethical guide lines. All biochemical assays were carried out by the standard kit methods. A marked increase in plasma levels of fasting blood sugar, lipid profile accompanied with increase in the lipids and apo-protein levels of serum β lipoproteins following decrease in lipid and protein constituents of α lipoprotein were noted in type 2 diabetic patients compared to healthy controls. The results after prescription of *Tinospora cordifoia* (powered stem; 50 mg/kg body weight, p. o.) for 15 days in type 2 diabetic patients resulted significant decrease in the level of fasting blood sugar, total cholesterol, β lipoproteins and triglycerides. The decrease in lipids and apoprotein levels of β lipoproteins was accompanied with stimulation of plasma lecithin cholesterol acyltransferase (LCAT). Lipid and apoprotein level of α lipoproteins were also recovered partially. Results of this study may provide scope for further research and leading to development of a potent anti diabetic, antidyslipoproteinemic anti oxidant drug from *Tinospora cordifolia* (*T. cordifolia)* stem.

INTRODUCTION: Type 2 Diabetes Mellitus (T2DM) is a cluster of abnormal metabolic paradigms with the essential feature of hyperglycemia and is dubbed as the disease of "premature ageing".

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Incidence of T2DM is rising all over the world at worrying rate, despite, comprehensive and coordinated effects of World Health Organization (WHO), International Diabetes Federation and Several Social Science Agencies [1].

All efforts have failed till date to arrest this rising incidence. 6.6 % of the world population was affected by this disease in 2010 with an estimated 285 million carriers and the number may become almost double (552 million) by 2030. India is facing an even more grim scenario. In 2000, the number of diabetic carriers was 31.7 million which

rose to 58.7 million in 2010 and 12 million more patients are expected to get added in another 20 years. On the basis of affected population, both in terms of percentage and numbers India has significantly more patients than China and other neighbouring countries and is often referred to as the diabetic capital of the world. The reasons for this lopsided proclivity are still poorly understood [2].

There is an urgent need for more intensive research to investigate the cure and control of this disease in the world, and in India in particular. In all probability, this has led to further prevalence and dependence on the ancient traditional medical system of Ayurveda, which is in practice since ancient times and has progressively to been enriched over centuries by learned practioners. The benefits of Ayurveda, an ancient system of traditional medicine are now well recognized. Interestingly, many drugs of modern medicine derive their origin from plant sources. Among the many beneficial herbal plants, *Tinospora cordifolia* (*T. cordifolia*) "Giloy" stands out as an exceptional source with a multitude of medicinal benefits [3].

It has widely been used for many diseases such as diabetes, hepatitis, cancer, Parkinson's disease, inflammatory arthritis and neurological disorders, either alone or in combination with other Ayurvedic medicines. It can be used either as a whole plant or different parts can be used in isolation. We have recently revalidated its beneficial effects in the management of hyperglycemia, dyslipidemia and oxidative stress in alloxan induced diabetic rats [4]. Metabolically, T2DM is a hetrogenous multifactorial syndrome with environmental and pleotropic involvement in which the former are overwhelmingly significant factors. Indeed, hyperglycemia is an essential expression due to relative or absolute lack of insulin action or secretion.

Pathway selective insulin resistance is a cardinal, if not essential feature. It is almost inevitably accompanied with hyperglycemic complexities such as altered lipid metabolism and raised oxidative status due to unfavorable "Cellular Redox Homeostatic Box". Several researchers have corroborated this condition by animal cell culture and *in vitro* studies and our recent animal studies also support them. Sangeetha et al., 2011 reported that *T. cordifolia* attenuated oxidative stress and improved glycemic level by improving insulin secretion in rats [5]. Umamaheswari and Mainzen (2007) reported that an Ayurvedic formation ILOGEN EXCEL improved blood sugar level in rats. This Ayurvedic drug containing *T. cordifolia* has shown an impressive performance in this regard [6]. Recently Vishnu Kumar et al., (2013), examined the effect of *T. cordifolia* stem administration in alloxan treated diabetic rats and noted that it helped to reverse hyperglycemia, dyslipiproteinemia and oxidative stress [4]. In view of the above considerations the present study was carried out to assess the effect of *T. cordifolia* in diabetic patients.

MATERIAL AND METHODS:

Selection of Healthy Human Volunteers:

30 healthy control (Male-15, Female-15), age 47 to 57 years, BMI 18-22.9 were served as Control. These individuals attended the outpatient department for their periodical health checkup.

Selection of Diabetic Subjects:

60 type 2 diabetic subjects (Male-30, Female-30) were selected from Diabetes Outpatient Department of, Kaya Chikitsha Vibhag, Rajkiya Ayurvedic Chikitsha Mahavidyalaya, Touriya Ganj, Lucknow. This research program was approved by the Ethical Committee of Rajkiya Ayurvedic Chikitsha Mahavidyalaya, Touriya Ganj, Lucknow - 226003.

Exclusion Criteria: Patients with evidence of acute or chronic inflammatory conditions, infectious disease, hypertension, cancer, persons on insulin or other medications that could affect glucose metabolism were excluded. Pregnant and lactating women were also not included in the study.

Inclusion Criteria: All diabetic individuals were subjected to a complete medical evaluation by a physician including recording a full medical history and physical examination. Both males and females between 47 - 57 years of age, BMI 23-24.9, fasting blood glucose 135 – 150 mg/dl, were included in the study.

Study Design:
Subjects were divided in to three groups of 30 subject each, with the following conditions:

Group 1: Healthy Control: 20 minute brisk walk/day with Balance Diet

Group 2: Diabetic Control: 20 minute brisk walk/day with low carbohydrate Diet

Group 3: Diabetic treated: 20 minute brisk walk/day, low carbohydrate diet with *T. cordifolia* stem powder (50 mg/ kg body weight/ day/ oral macerate with water). This study was run for 15 days.

Collection of blood samples:
Fasting blood samples were collected, before and after the study period, from the ante median cubital vein of the subjects following overnight fasting, using disposable plastic syringes with all aseptic precautions. Blood was transferred immediately in to a dry clean plastic test tube with a gentle push to avoid hemolysis. Blood was collected from all three groups, for biochemical estimations in fluoride (sodium fluoride and potassium oxalate, 5.4 mg NaF and 3.0 mg K-oxalate in each vial), EDTA (3 mg/ vial) and plain vials.

Separation of serum and plasma:
Plasma was separated by centrifuging anticoagulant mixed whole blood at 1500 rpm for 15 minutes at 4 °C in Eppendorf centrifuge machine. On the other hand, for separating serum, the whole blood was kept in plain vacuutainer at 37 °C for 30 minutes after which this coagulated blood was centrifuged at 1500 rpm for 15 minute at 4°C in Eppendorf centrifuge machine. The supernatant was pipette out in a new tube and kept at - 20 °C till analysis.

Preparation of RBC lysate:
3 ml whole blood of EDTA vacuutainer was taken and centrifuged at 1500 rpm for 15 minutes at 4 °C in Eppendorf centrifuge machine. The whole supernatant from the tubes was pipette out, and then added 1 ml of normal saline (0.9% Nacl, isotonic solution). It was then again centrifuged at 1500 rpm for 15 minutes at 4°C in Eppendorf centrifuge machine. This step was repeated for three times for proper washing of RBC. Then 1.0 ml of washed RBC was taken in a new test tube, to which 3 ml of chilled Tripled Distilled Water (TDW) was added to lyses RBC. It was mixed/shaked well for 1 minute. This step followed by centrifugation at 10,000 rpm for 15 minutes at 4°C in Eppendorf centrifuge machine to settle down cell ghost of RBC. The supernatant was pipette out in a new tube and stored it at -20°C till analyzed.

Preparation of plant stem powder:
Healthy (free from diseases as well as insecticidal & pesticidal effects) *T. cordifolia* stems were collected from local area of Lucknow, checked and identified taxonomically with the help of Taxonomist and plant pathologist of Department of Pharmacology, Era's Lucknow Medical College & Hospital, Lucknow and a voucher specimen was also submitted (TC-001/06). Stems were dried under shade and made into fine powder using laboratory mill [4].

Biochemical analysis of blood and plasma:
The blood was centrifuged and plasma was separated. The fasting blood sugar (FBS) [7] was analyzed in plasma while glycosylated hemoglobin (HbA1C) [8], Super oxide dismutase (SOD) [9], Catalase (CAT) [10], Glutathione peroxidase (GPx) [11] and Glutathione reductase (GR) [12] were estimated in RBC lysate, serum totalcholesterol (TC) [13], triglyceride (TG) [14], high density lipoprotein total cholesterol (HDL-TC) [15] were assayed by standard spectrophotometric methods. Low density lipoprotein total cholesterol (LDL-TC) and very low density lipoprotein total cholesterol (VLDL-TC) were calculated by Friedewald's equation [16]. Serum was also used for the assay of lecithin cholesterol acyl transferase activity (LCAT) [17], lipid peroxide (LPO) [18], and reduced glutathione (GSH) [19]. A portion of serum was fractionated into very low density lipoprotein (VLDL), low density lipoprotein (LDL) and high density lipoprotein (HDL) by polyanionic precipitation methods [20]. Lipoproteins were measured for their total cholesterol (TC) [13], phospholipids (PL) [21], triglyceride (TG) [14] and apoprotein [22] by standard spectrophotometric methods.

Statistical analysis: One-way-analysis of variance (ANOVA- Newman's student test) was performed by comparison of values for diabetic group with

control, diabetic and *T. cordifolia*-treated with diabetic group. All hypothesis testing were two-tailed. P <0.05 was considered statistically significant and the results were expressed as mean ± SD. The Graph pad INSTAT 3.0 software was used to carried out the statistical analysis [23].

Results:

Effect of *T. cordifolia* stem powder on fasting blood sugar, HbA1c, LCAT and serum lipid profile in type 2 diabetic patients: The data in **Table 1** shows that, in type 2 diabetic patients showed markedly increased levels of in fasting blood sugar 57 %, HbA1c 40 %, serum; TC, TG, LDL- Cholesterol and VLDL- Cholesterol levels 34%, 59%, 58 %, 60 % respectively. On the other hand type 2 diabetic patients showed decreased levels of HDL- Cholesterol by 39% and LCAT levels17%. As compared to healthy controls, however, treatment with *T. cordifolia* stem powder caused reversal in the levels; fasting blood sugar by 9 %, HbA1c 14 %, TC 13%, TG 18%, LDL-TC 11%, VLDL-TC 18%. There was increase in the level of HDLTC 12 % and LCAT activity 8%.

TABLE 1: EFFECT OF *T. CORDIFOLIA* STEMS POWDER ON FASTING BLOOD SUGAR, GLYCOSYLATED HEMOGLOBIN, SERUM LECITHIN CHOLESTEROL ACYL TRANSFERASE AND SERUM LIPID PROFILE IN TYPE-2 DIABETIC PATIENTS.

Experimental schedule	BMI (Kg/m^2)	Fasting Blood sugar	Glycosylated Hemoglobin (g%)	Serum LCAT (mmol/L/hr)	Serum lipid profile				
					TC (mg/dl)	TG (mg/dl)	LDL-TC (mg/dl)	VLDL-TC (mg/dl)	HDL-TC (mg/dl)
Healthy Control	18-22.9	92.26 ± 9.05	4.98 ± 0.53	79.54 ± 14.97	200.26 ± 21.67	110.06 ± 20.18	127.24 ± 24.57	21.89 ± 7.56	49.80 ± 9.17
Type 2 Diabetic Control	23-24.9	144.40 ± 10.86*** (+ 57%)	6.95 ± 0.78*** (+ 40%)	65.78 ± 13.18*** (- 17%)	268.53 ± 11.36*** (+34 %)	175.00 ± 28.01*** (+59 %)	201.17 ± 14.42*** (+58 %)	35.00 ± 5.60*** (+60%)	30.53 ± 4.44*** (-39%)
Type 2 Diabetic+ *T. cordifolia* (50 mg/kg b.w. p.o.)	23-24.9	130.97 ± 14.14** (-9%)	5.87 ± 0.83NS (- 14%)	71.23 ± 12.74 (+8%)	237.46 ± 13.77* (-13%)	143.23 ± 23.64** (-18%)	178.79 ± 17.10NS (-11%)	28.60** ± 4.85** (-18%)	34.76 ± 4.36NS (+12.0%)

Values expressed as mg/dl are mean ± SD of 30 subjects. Values in the parenthesis are percent change. Type 2 Diabetic Control is compared with Healthy Control, and type 2 diabetic treated group with type 2 diabetic. ***p<0.001, **p<0.01,* p<0.05, NS= Non significant.

Effect of *T. cordifolia* stem powder on serum lipoprotein profile in type 2 diabetic patients: Analysis of hyperglycemic serum (Table 2) showed marked increase in the levels of lipids and apoprotein constituting β-lipoproteins (VLDL and LDL) and these effects were pronounced for VLDL-TC 60 %, PL 133 %, TG 59 % and apoproteins 7 %. There was increase in LDL-TC, PL, TG 62 %, 139 %, 23 % respectively and apoprotein 13 %. There was a decrease in HDL-TC, PL, TG and apoprotein (34 %, 24 %, 10 % and 25 %) respectively. The data in **Table 2** also show that treatment with *T. cordifolia* stem powder for 15 days significantly decrease in the level of VLDL-TC 18 %, PL 22 % TG 14 %, and Apoprotein 4 % and same trend of decrease in levels of LDL-TC 11 %, PL 24 %, TG 23 %, and apoprotein 5%. At the same time *T. cordifolia* stem powder showed an increase in the levels of HDL-TC, PL, TG and apoprotein 7%, 7 %, 10 % 9 %respectively.

TABLE 2: EFFECT OF *T. CORDIFOLIA STEMS* POWDER ON SERUM LIPOPROTEIN PROFILE IN TYPE-2 DIABETIC PATIENTS

Experimental schedule	VLDL				LDL				HDL			
	TC (mg/dl)	PL (mg/dl)	TG (mg/dl)	Apo-protein (mg/dl)	TC (mg/dl)	PL (mg/dl)	TG (mg/dl)	Apo-protein (mg/dl)	TC (mg/dl)	PL (mg/dl)	TG (mg/dl)	Apo-protein (mg/dl)
Control	21.89 ± 7.56	37.50 ± 3.99	39.10 ± 3.95	16.85 ± 1.04	124.16 ± 14.42	29.55 ± 2.11	27.12 ± 1.11	27.13 ± 1.61	46.80 ± 9.17	82.55 ± 9.35	18.47 ± 1.79	183.83 ± 11.34
Type 2 Diabetic	35.00 ± 5.60*** (+ 60 %)	87.50 ± 7.48*** (+ 133 %)	58.76 ± 5.70*** (+ 59 %)	18.00NS ± 0.57 (6.8 %)	201.17 ± 14.42*** (+ 62 %)	70.59 ± 7.43*** (+ 139 %)	33.21 ± 6.29*** (+ 23 %)	30.55 ± 1.46* (12.6 %)	30.53± 4.44*** (- 34%)	62.52 ± 6.27*** (- 24.26 %)	16.55 NS ± 1.28 (-10.39 %)	137.42± 12.33*** (-25.31%)

Type 2 Diabetic + *T. Cordifolia* (50 mg/kg b.w.)	28.60 ± 4.85** (- 18%)	68.18 ±6.51*** (- 22%)	50.29 ±4.85* (- 14%)	17.36 NS ±6.80 (- 3.5%)	178.79 ±17 .0* (- 11%)	53.41 ±4.90*** (- 24%)	25.66 ±4.28*** (- 23%)	28.90 ±1.44 NS (- 5%)	32.76 ±4.36 NS (+ 7%)	66.82 ±2.90 NS (+ 7%)	18.25 ±1.25 NS (+ 10%)	149.80 ±13.27 NS (+ 9%)

Values are expressed as mean ± SD of 30 subjects, Type 2 Diabetic group was compared with control, Type 2 Diabetic and drug-treated groups with Type 2 Diabetic. ***p<0.001, **p<0.01, *p<0.05, NS= Non significant

Effect of *T. cordifolia* stem powder on GSH, LPO, SOD, Catalase, GPx and GR in type 2 diabetic patients

The data in **Table 3** show that in type 2 diabetic patients there was decrease in the levels of GSH, SOD, CAT by 49 %, 24%, 11 % respectively and increase in level of plasma LPO by 252 %. Treatment with *T. cordifolia* stem powder for 15 days showed the reversal of results by increasing the levels of GSH, SOD, Catalase, GPx and GR by 36 %, 37 %, 17 %, 11 % and 37 % while the levels of LPO decreased by 42%.

TABLE 3- EFFECT OF *T. CORDIFOLIA STEMS* POWDER ON GSH, SERUM LIPID PEROXIDE; SOD, CATALASE, GPX AND GR IN TYPE-2 DIABETIC PATIENTS

Experimental schedule	Status of markers used for oxidative stress in Serum		Status of Antioxidant Enzymes in RBC Lysate			
	GSH (mg/ dl)	Lipid peroxide (nmol MDA/ml)	SOD (Unit/minute/ mg protein)	Catalase (Unit/minute/mg protein)	GPx (n mole NADPH Oxidized/min/mg protein)	GR (n mole NADPH Oxidized/min/mg protein)
Control	38.56 ± 3.76	2.17 ± 0.36	2.78 ± 0.19	3853 ± 251.36	366.38±160.00	245.00±34.88
Type 2 Diabetic	19.79±1.63*** (- 49%)	7.65 ± 1.36*** (+253%)	2.12 ± 0.18NS (-24%)	3432 ± 267.08NS (-11%)	280.00±87.56 (-24%)	145.00±38.13 (-41%)
Type 2 Diabetic + *T. Cordifolia* (50 mg/kg b.w.)	27.00 ± 1.31NS (+ 36%)	4.41 ± 1.18*** (-42%)	2.91 ± 0.23*** (+ 37%)	3997 ± 302.23** (+17%)	310.00±77.33 (+11%)	197.66±34.88 (+37%)

Values are expressed as mean ± SD of 30 subjects, Type 2 Diabetic group was compared with control, Type 2 Diabetic and drug-treated groups with Type 2 Diabetic. ***p<0.001, **p<0.01, *p<0.05, NS= Non significant.

DISCUSSION: Diabetes mellitus, as explained earlier, is a highly stressful disease. If detected early it can be controlled through diet and exercise, but in later stages drugs become inevitable. In India which is reeling under population distress, and where more than one third of the population lives below the poverty line with another one third subsisting on compromised economic conditions, regular health check up is not always possible due to financial constraints, lack of health awareness and inadequate health infrastructure. Consequently in most of the patients T2DM is detected quite late sometimes even 10-20 years after onset [24]. Therefore, in the Indian context, diet and exercise become almost futile in most of freshly detected patients who usually require immediate therapeutic intervention.

Due to economic compulsions, many patients cannot afford modern medicines. Moreover, most of the modern (allopathic) medicines in T2DM have undesirable side effects; and no single drug can treat all the multifarious problems with rectitude. In search of a patient's lean on other traditional systems of medicines and indeed Ayurveda is one of the most popular systems in India for several reasons. Ayurveda has a centuries old tradition of Ayurvedic practitioners, saints and sages, and largely relies on medicinal herbs which are either available at low cost or available free in fields and gardens. Proven use of these herbs over many centuries certifies item non toxic with no side effects.

We administered the shade dried stem of this plant in hyperglycemic patients for two weeks. Let us explain rationale for two week limited prescription therapy. First, it did not seem ethically prudent to keep controls on diet and exercise alone for longer period because lack of any previous health examination and tests the hyperglycemia may be persisting for a prostrated period. Second, in view

of its highly acclaimed value in Ayurveda and proven value in experimental animals and robust in *in vitro* studies [25]. It was *T. cordifolia* that even a short term clinical trial may show some discern able trends. Interestingly the results are very encouraging.

In the present study the average glycosylated hemoglobin (HbA1c) was significantly higher in patients when compare with control ($p < 0.001$) and so was the fasting blood sugar level, total cholesterol, LDL cholesterol, VLDL cholesterol and triglycerides levels. On the contrary shown HDL cholesterol level and lecithin cholesterol acyl transferase activity (LCAT) were significantly lower. These observations clearly indicated that in these diabetic patient's lopsided dyslipidemia also existed. Numerous studies in literature corroborate these observations. *T. cordifolia* therapy even for two weeks showed a very positive trend. Blood sugar levels were significantly decreased ($p<0.01$), though these still remained slightly raised values in some patients. In fact it is a good sign because steep fall in blood sugar level is not recommended. Mean glycosylated hemoglobin level was on upper side of normal (7.0 g%).

Although *T. cordifolia* therapy did not significantly decrease the glycated Hb but it also showed a definite declining trend. Similarly dyslipidemia also seemed to be on the course to correction. Total cholesterol ($p<0.05$), VLDL cholesterol ($p<0.01$), triglyceride ($p<0.01$), showed, significant reduction trend. Glycosylated Hb, LDL cholesterol showed non-significant declining trend. HDL cholesterol showed a very mild increasing trend, which is not a very cheering sign. May be better results are obtained in a long term studies. In another exercise subfraction (total cholesterol, phospholipids, triglycerides and apoprotein fractions) of VLDL, LDL and HDL were examined. While lipid fractions were adversely affected in patients and required correction, the three most important features needing focus are low HDL cholesterol, low LCAT levels (**Table 2**) and low HDL apoprotein fraction (**Table 3**). There is consistent evidence that HDL choledterol is a potent predictor of cardiovascular events independently and also in T2DM patients [26]. The cardio protective effect of HDL is attributed to its role in reverse cholesterol transport. It removes excess cholesterol from peripheral tissues towards the liver for excretion in to bile or else for steroid hormone synthesis in steroidogenic organs.

Further effects of HDL are proteotropic as it also exerts most importantly as antioxidant and anti-inflammatory agent [24]. Lecithin cholesterol aceyl transferase is an vitally important enzyme helping in reverse cholesterol transport. It transfers 2 acyl groups of lecithin to cholesterol resulting in generation of cholesterol esters which are retained in core of HDL particle for final scavenging. Incidentally glycosylated Hb negatively correlates with LCAT activity in T2DM. Apoprotein-1 is quantitatively a major component of HDL. Glycation of apoprotein A-1 in HDL alters and reduces LCAT activity in proportion to the extent of apoprotein A-1 glycation. Indeed there is convincing evidence that hyperglycemia induces several pathways generating more ROS. These ROS increase glycation potential [22].

In our study, apoprotein-1 significantly decreased (25.31%; $p<0.01$) and concomitantly OS also incresesd by 25.30% ($p<0.01$). Further more in both VLDL and LDL fractions total cholesterol and triglycerides level were consistently and considerably higher in diabetic patients indicating dyslipidemia. It is now widely accepted that dyslipidemia is a cardinal feature in dibetes**.** American Diabetes Association, 2003, had stated that T2DM is associated with a cluster of interrelated plasma lipid and lipoprotein fractions. Low HDL and elevated triglycerides also increase the risk of cardiovascular disease 2 -4 times in T2DM [25].

Although cells usually exist with reductive environment, but oxidation and reduction reactions are essential and crucial phenomenon of every cell. In normal cells at any given time oxidative processes yielding Reactive oxygen species (ROS) are slightly more than reduction processes. This oxidative potential is termed as OS. ROS and antioxidants are major determinant of oxidative stress (OS) as other cellular oxidative reductive processes are in balance. OS is raised in T2DM through numerous pathologies.

Although the role of OS in origin of T2DM is still controversial issue but it definitely abets T2DM and plays a central role in development of diabetic complications. One of the major oxidant is super oxide anion, that too with predominance in endothelial cells of both large and small arteries and myocardium and in convenience with dyslipidemia it increases the risk of cardiovascular events several folds. It is also postulated that O2 inactivates 2 critical artiatherosclerotic enzymes endothelial nitric oxide synthase and prostacyclin Synthase [26]. In the present study, LPO, an accepted marker of OS in T2DM was significantly raised in diabetic patients. The average increase was more than threefold to that of controls. This clearly alluded and signified to provoke OS in diabetes. Consequently this must be disturbing the redox box.

The raised OS was accompanied with reduction in GSH level (49%), and lower SOD (24%), Cat (11%), GPx (24 %) and GR (41%) activities.

On the contrary endogenous antioxidants are receiving increasingly favorable support and alteration they are reducible and try to balance cellular antioxidants, thereby maintaining cellular redox homeostasis [27]. In light of these report, the observation stated in **Table 3** purport perturbed redox box in T2DM. *T. cordifolia* administration for two weeks showed a very promising picture. Two weeks administration of this herb decreased the LPO level by 42% ($p<0.001$) concomitantly the level of five endogenous antioxidant GSH (37%), SOD (37%), catalase (17%), GPx (11%) and GR (37%) increased. A dramatic attenuation of OS signifies an overall improve coverage by endogenous antioxidant as no supplement of exogenous antioxidant was given not alteration in diet was suggested. In conclusion *T. cordifolia* therapy could prove an excellent substitute for multidrug therapy which is currently recommended for management of T2DM. Moreover, most importantly this herb does not have any side effects [4].

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