RESULTS AND DISCUSSION PHASE III

PHASE III (A) PHYTOCHEMICAL PROFILE OF TINOSPORA CORDIFOLIA

The phytochemical screening of pure extract of Tinospora cordifolia stem yielded the presence of the following bioactive compounds; tannins, alkaloids, flavonoids, terpenoids and cardiac glycosides. However, saponins and steroids were absent.

PHASE III (B) IMPACT OF TINOSPORA CORDIFOLIA SUPPLEMENTATION IN THE MANAGEMENT OF DIABETIC DYSLIPIDEMIA

General Profile

The age of type 2 diabetic dyslpidemics was similar in both the arms; however, diabetics in the experimental arm had non-significantly higher duration of diabetes (table 4.115). A higher proportion of males (55.2%) in the experimental arm and females (56.7%) in the control arm were part of the research, respectively. According to the age distribution, 51.7% type 2 diabetics in the intervention arm and 56.7% in the control arm belonged to the 50 to 60 years age bracket and the least proportion of participants were in the 40-50 years age bracket.

Family Disease Profile of Non-Communicable Diseases

A higher proportion of type 2 diabetics from the intervention arm had a family history of diabetes (55.2% vs. 36.7%), hypertension (55.2% vs. 43.3%) and adverse cardiac events (34.5% vs. 16.7%) compared to those from the control arm. However, the proportion of type 2 diabetics with a family history of cancer was higher in the control arm than the intervention arm (10% vs. 6.8%).

Disease and Drug Profile

About 75.8% of the type 2 diabetics in the intervention arm had clinically confirmed hypertension compared to 63.3% in the control arm. However, the prevalence of adverse cardiac events was similar in both the groups (13.3% and 1.7%). All the type 2 diabetics were on OHAs and dyslipidemic agent (statin). Though non-significant, more of the intervention arm subjects were on calcium channel blockers, anti-anginal agents and thyroid hormones. (table 4.116).

Diet Profile and Nutrient Intake

Majority of the subjects in both the arms were vegetarians, 63.3% in controls and 58.6% in the intervention arm. The remaining of the subjects had non-vegetarian habits.

Cottonseed oil was the most commonly consumed oil by the participants in both the arms (20.6% experimental group and 26.7% control group), followed by rice bran in the control arm and olive oil in the experimental arm.

At baseline, subjects of the supplementation group had non-significantly lower energy intake along with that of proteins, carbohydrates and potassium than the controls. Calcium intake reduced significantly in the intervention arm from 656.2mg to 588.2mg (P 0.014) and protein intake reduced significantly from 41.2g to 38.9g (P 0.001) among controls (table 4.117).

Physical Activity Profile

At pre and post intervention and between groups, there was no significant difference in the physical activity profile of the two groups. The subjects in both the arms had moderate physical activity profile based on average METminutes/week score (table 4.118 and fig 4.64).

TABLE 4.115: GENERAL PROFILE OF TYPE 2 DIABETICS WITH DYSLIPIDEMIA (MEAN ± SD, N, %)

Variables	Control Group (N=30)	Experimental Group (N=29)	P Value
Age (years)	54.8 ± 6.4	54.9 ± 7.3	0.97
40-50 years	5 (16.6)	6 (20.6)	0.69
50-60 years	17 (56.7)	15 (51.7)	0.70
60-70 years	8 (26.6)	8 (27.5)	0.93
Duration of diabetes (years)	6.5 ± 5.2	7.6 ± 6.5	0.47
Males	13 (43.3)	16 (55.2)	0.36
Females	17 (56.7)	13 (44.8)	0.36

p<0.05*, p<0.01**, p<0.001***, values in parenthesis indicate percentage

TABLE 4.116: DRUG PROFILE OF TYPE 2 DIABETICS WITH DYSLIPIDEMIA (N, %)

Drugs	Control Group (N=30)	Experimental Group (N=29)	P value
Oral hypoglycaemic drugs	30 (100)	29 (100)	1
Statin	30 (100)	29 (100)	1
Calcium antagonist agents	4 (13.3)	9 (31)	0.10
Anti-anginal agents	2 (6.6)	7 (24.1)	0.07
Anti-platelet agents	8 (26.6)	7 (24.1)	0.82
Thyroid hormones	3 (10)	7 (24.1)	0.18
Angiotensin II antagonist agents	10 (33.3)	11 (37.9)	0.71
Beta blocker agents	8 (26.6)	5 (17.2)	0.38
NSAID agents	4 (13.3)	3 (10.3)	1

Values in parenthesis indicate percentage

TABLE 4.117: NUTRIENT INTAKE OF TYPE 2 DIABETICS WITH DYSLIPIDEMIA (MEAN±SD)

Nutrients	Stage	Control Group (N=30)	Experimental Group (N=29)	P value
Energy (kcal)	Pre	1417 ± 255	1376 ± 234	0.51
	Post	1388 ± 228	1367 ± 184	0.68
	Paired t	0.06	0.66	
Carbohydrates (g)	Pre	192.2 ± 51	178.8 ± 39.1	0.26
	Post	197.5 ± 41.7	185.8 ± 29.1	0.27
	Paired t	0.10	0.10	
Fat (g)	Pre	49.6 ± 13.7	52.7 ± 11.9	0.36
	Post	47.1 ± 11.5	53.5 ± 10.2	0.12
	Paired t	0.09	0.51	
Protein (g)	Pre	41.2 ± 9.7	38.1 ± 8.4	0.20
	Post	38.9 ± 8.03	36.1 ± 9.5	0.24
	Paired t	**0.001****	0.13	
Calcium (mg)	Pre	596.8 ± 243.3	656.2 ± 287.8	0.39
	Post	551.1 ± 213.6	588.2 ± 249.9	0.54
	Paired t	0.059	**0.014***	
Vitamin C (mg)	Pre	59.8 ± 41.6	73.2 ± 62.3	0.33
	Post	55.5 ±31.4	65.7 ± 46.1	0.32
	Paired t	0.10	0.08	
Sodium (mg)	Pre	115.2 ± 29.2	126.5 ± 58.5	0.69
	Post	121.7 ± 39.1	122.3 ± 46.1	0.91
	Paired t	0.48	0.40	
Potassium (mg)	Pre	1147.8 ± 329	1080.2 ± 300.6	0.21
	Post	1101 ± 431	1045.4 ± 297.8	0.10
	Paired t	0.10	0.18	
Total dietary fibre (g)	Pre	11.4 ± 4.3	12.5 ± 5.4	0.31
	Post	11.2 ± 4	12.1 ± 4.6	0.42
	Paired t	0.11	0.22	

$p<0.05$*, $p<0.01$**, $p<0.001$***

TABLE 4.117: NUTRIENT INTAKE OF TYPE 2 DIABETICS WITH DYSLIPIDEMIA (MEAN±SD)

Nutrients	Stage	Control Group (N=30)	Experimental Group (N=29)	P value
Insoluble dietary fibre (g)	Pre	8.6 ± 3.2	9.8 ± 4.3	0.29
	Post	8.4 ± 3.03	9.2 ± 3.5	0.35
	Paired t	0.19	0.27	
Soluble dietary fibre (g)	Pre	2.83 ± 1.1	3.4 ± 2.1	0.46
	Post	2.8 ± 1.01	2.9 ± 1.1	0.69
	Paired t	0.79	0.27	

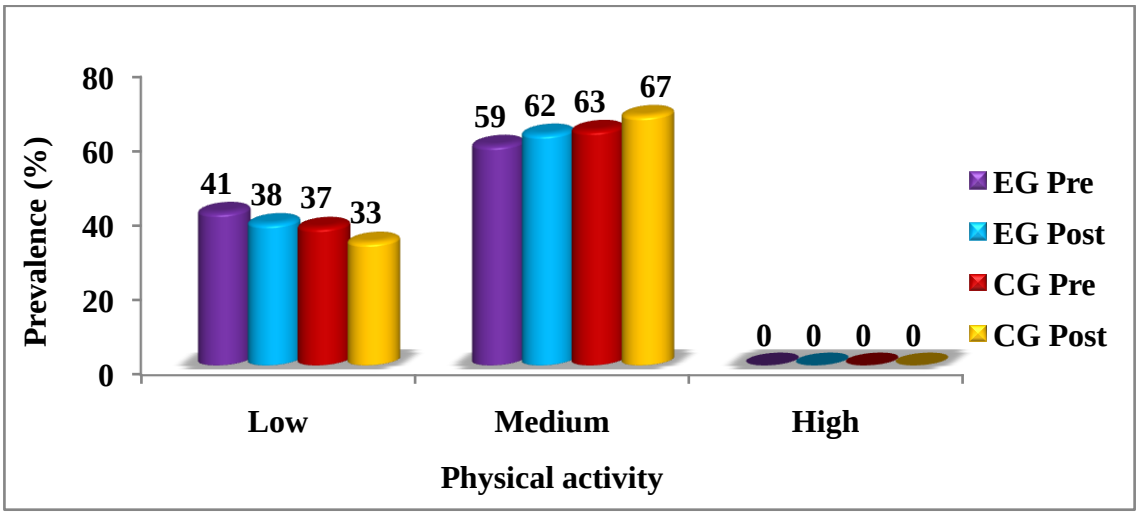
p<0.05*, p<0.01**, p<0.001***

TABLE 4.118: PHYSICAL ACTIVITY STATUS OF TYPE 2 DIABETICS WITH DYSLIPIDEMIA (MEAN ± SD)

Variables	Stage	Control Group (N=30)	Experimental Group (N=29)	P Value
Total METminutes/week	Pre	943 ± 596	948.9 ± 515.6	0.96
	Post	948.2 ± 564.9	945.2 ± 503	0.98
	Paired t	0.78 (↑0.55%)	0.89 (↓0.38%)	

p<0.05*, p<0.01**, p<0.001***, values in parenthesis indicate percentage

FIG 4.64: PHYSICAL ACTIVITY PROFILE OF TYPE 2 DIABETICS WITH DYSLIPIDEMIA (%)



IMPACT OF TINOSPORA CORDIFOLIA SUPPLEMENTATION

Impact on Anthropometric and Blood Pressure Profile

The intervention led to a non-significant decline in weight and BMI. However, the two parameters did not differ significantly either between or within the groups. WC by 0.52% (94.7 to 94.2 cm, P 0.004), HC by 0.4% (99.9 to 99.5 cm, P 0.004) and WSR by 0.5% (0.594 to 0.591, P 0.004) declined significantly post intervention in the experimental arm, whereas only HC had a significant decline in the control arm by 0.31% (100.02 to 99.7 cm, P 0.01). SBP declined significantly in experimental arm by 4.1% (132.6 to 127.1 mmHg, P 0.017) as well as in the control arm by 3.3% (134.5 to 130.1 mmHg, P 0.013) post treatment (table 4.119).

Impact on Nutritional Status

The proportion of type 2 diabetics with a normal BMI, overweight and obese remained static in the control arm. However, subjects with a normal BMI increased (13.7% to 17.2%) and the prevalence of overweight declined (24.1% to 20.6%) in the experimental arm post intervention. The prevalence of elevated WC dropped from 86.2% to 82.7% and that of WSR from 79.3% to 72.4% in the intervention arm and no changes were observed in the prevalence in the controls (fig 4.65).

Impact on Renal Profile

BUN and creatinine declined non-significantly after the intervention and the values did not differ between the groups. However, uric acid not only declined significantly post intervention from 5.2 to 4.6mg/dl (P 0.007), but was also significantly lower than the control arm's post treatment value (5.7 to 4.6 mg/dl, P 0.0018). Calcium declined significantly in the experimental arm post treatment from 9.5 to 9.4mg/dl (P 0.036) and a non-significant decline was observed in the control arm (table 4.120).

TABLE 4.119: IMPACT OF TINOSPORA CORDIFOLIA SUPPLEMENTATION ON ANTHROPOMETRIC AND BLOOD PRESSURE PROFILE OF TYPE 2 DIABETICS WITH DYSLIPIDEMIA (MEAN ± SD)

Variables	Stage	Control Group (N=30)	Experimental Group (N=29)	P Value
Weight (kg)	Pre	69.7 ± 11.2	68.7 ± 10.9	0.74
	Post	69.1 ± 11.4	68.2 ± 11.1	0.65
	Paired t	0.53 (↓0.86%)	0.07 (↓0.72%)	
Height (cm)		157.6 ± 9.5	159.6 ± 7.9	0.39
Body mass index (kg/m^2)	Pre	28.3 ± 5.8	27.01 ± 4.1	0.31
	Post	28.2 ± 5.8	26.8 ± 4.3	0.25
	Paired t	0.53 (↓0.35%)	0.081 (↓0.77%)	
Waist circumference (cm)	Pre	95.7 ± 11.1	94.7 ± 9	0.69
	Post	95.5 ± 11	94.2 ± 9.1	0.62
	Paired t	0.16 (↓0.2%)	**0.004** (↓0.52%)**	
Hip circumference (cm)	Pre	100.02 ± 9.2	99.9 ± 9.8	0.96
	Post	99.7 ± 9.07	99.5 ± 9.6	0.93
	Paired t	**0.01** (↓0.31%)**	**0.004** (↓0.4%)**	
Waist stature ratio	Pre	0.61 ± 0.08	0.594 ± 0.06	0.41
	Post	0.60 ± 0.08	0.591 ± 0.06	0.37
	Paired t	0.17 (↓1.6%)	**0.004** (↓0.5%)**	
Waist hip ratio	Pre	0.95 ± 0.06	0.94 ± 0.02	0.50
	Post	0.95 ± 0.06	0.94 ± 0.03	0.42
	Paired t	0.94 (0%)	0.23 (0%)	
Systolic blood pressure (mmHg)	Pre	134.5 ± 13.8	132.6 ± 9.9	0.55
	Post	130.1 ± 10.04	127.1 ± 6.9	0.17
	Paired t	**0.0013** (↓3.3%)**	**0.0017** (↓4.1%)**	
Diastolic blood pressure (mmHg)	Pre	84.7 ± 7.2	86 ± 6.1	0.48
	Post	86.7 ± 4.3	84.9 ± 5.1	0.15
	Paired t	0.17 (↑2.4%)	0.28 (↓1.3%)	

$p<0.05$*, $p<0.01$**, $p<0.001$***

FIG 4.65: IMPACT OF TINOSPORA CORDIFOLIA SUPPLEMENTATION ON NUTRITIONAL STATUS OF TYPE 2 DIABETICS WITH DYSLIPIDEMIA (%)

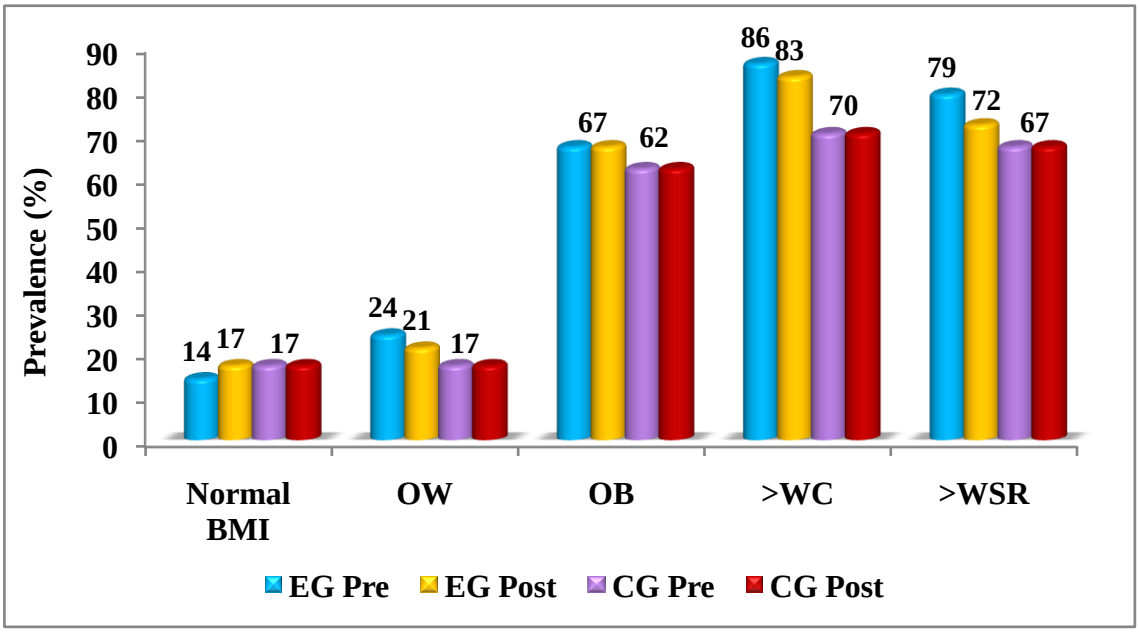


TABLE 4.120: IMPACT OF TINOSPORA CORDIFOLIA SUPPLEMENTATION ON RENAL PROFILE OF TYPE 2 DIABETICS WITH DYSLIPIDEMIA (MEAN ± SD)

Variables	Stage	Control Group (N=30)	Experimental Group (N=29)	P Value
BUN (mg/dl)	Pre	11.4 ± 4.1	10.9 ± 2.7	0.59
	Post	11.1 ± 3.5	10.5 ± 2.4	0.30
	Paired t	0.65 (↓2.6%)	0.24 (↓3.6%)	
Creatinine (mg/dl)	Pre	0.69 ± 0.2	0.7 ± 0.2	0.82
	Post	0.68 ± 0.15	0.69 ± 0.24	0.86
	Paired t	0.93 (↓1.4%)	0.81 (↓1.4%)	
Uric acid (mg/dl)	Pre	5.6 ± 1.2	5.2 ± 1.4	0.29
	Post	5.7 ± 1.1	4.6 ± 1.2	**0.0018****
	Paired t	0.87 (↑1.8%)	**0.007** (↓11.5%)**	
Calcium (mg/dl)	Pre	9.6 ± 0.34	9.5 ± 0.32	0.26
	Post	9.5 ± 0.28	9.4 ± 0.35	0.07
	Paired t	0.13 (↓1.04%)	**0.036* (↓1.05%)**	

p<0.05*, p<0.01**, p<0.001***

Impact on Lipid Profile

TC declined in both the arms after the intervention; by 14.5% in the experimental arm (208.3 to 178mg/dl, P 0.008) and by 6.8% in the control arm (188.2 to 175.4mg/dl, P 0.009). HDL-C remained unaltered within and between groups. LDL-C also declined significantly in both the arms, with the control arm having a mean 13.4% drop (112.6mg/dl to 97.5mg/dl, P 0.0012) and the experimental arm had a 13.6% drop (122.4mg/dl to 105.8mg/dl, P 0.0028). Triglycerides declined significantly by 14.9% (146.1mg/dl to 124.3mg/dl, P 0.036) in the experimental arm and by 16% in the control arm (154.6mg/dl to 129.9mg/dl, P 0.0017). VLDL-C declined significantly by 18.3% (28.9mg/dl to 23.6mg/dl, P 0.003) in the intervention arm and by 17.4% in the control arm (30.4mg/dl to 25.1mg/dl, P 0.010) (table 4.121).

Impact on Prevalence of Dyslipidemia

The prevalence of hypercholesterolemia declined by 24.12% from 55.2% to 31% with the intervention (P 0.065) and reduced by only 10% among the controls (36.7% to 26.7%) (fig 4.66). Prevalence of low HDL-C came down by 13.3% among controls from 56.6% to 43.3% (P 0.30) and reduced by only 3.5% among the intervention subjects, however the prevalence did not differ significantly between the two groups. The prevalence of elevated LDL-C came down more profoundly by 20.7% with the intervention (72.4% to 51.7%, P 0.10) and the controls had 13.3% decline (63.3% to 50%, P 0.30) and the prevalence between the two groups was almost similar at the end of the intervention. The prevalence of hypertriglyceridemia also came down more profoundly in the intervention arm subjects by 10.4% (37.9% to 27.5%) and reduced by only 3.3% among controls. In totality, the average number of dyslipidemic features came down more significantly with the intervention by 28.6% from 2.27 to 1.62 (P 0.0036) vs. 19.4% from 2.06 to 1.66 (P 0.020) among controls (table 4.122).

Impact on Lipid Ratios

The TC/HDL fraction declined significantly in the experimental arm by 14.6% (4.78 to 4.08, P 0.0002) and by 9.2% (4.24 to 3.85, P 0.018) in the control arm. LDL/HDL declined by 14.6% (2.81 to 2.4, P 0.0019) in the intervention arm and by 13.4% (2.54 to 2.2, P 0.002) in controls after the intervention (table 4.123).

TABLE 4.121: IMPACT OF TINOSPORA CORDIFOLIA SUPPLEMENTATION ON LIPID PROFILE OF TYPE 2 DIABETICS WITH DYSLIPIDEMIA (MEAN ± SD)

Variables	Stage	Control Group (N=30)	Experimental Group (N=29)	P Value
TC (mg/dl)	Pre	188.2 ± 38.2	208.3 ± 41.9	0.058
	Post	175.4 ± 37.8	178 ± 49.2	0.82
	Paired t	**0.009** (↓6.8%)**	**0.0008*** (↓14.5%)**	
HDL-C (mg/dl)	Pre	45.4 ± 9.3	45.6 ± 10.2	0.93
	Post	46.7 ± 11.1	45.3 ± 11.08	0.63
	Paired t	0.25 (↑2.9%)	0.80 (↓0.65%)	
LDL-C `(mg/dl)	Pre	112.6 ± 31.7	122.4 ± 38.01	0.28
	Post	97.5 ± 26.1	105.8 ± 37.1	0.33
	Paired t	**0.0012** (↓13.4%)**	**0.0028** (↓13.6%)**	
Triglycerides (mg/dl)	Pre	154.6 ± 65.06	146.1 ± 75.1	0.64
	Post	129.9 ± 48.1	124.3 ± 45.8	0.64
	Paired t	**0.0017** (↓16%)**	**0.036* (↓14.9%)**	
VLDL – C (mg/dl)	Pre	30.4 ± 12.7	28.9 ± 15.1	0.68
	Post	25.1 ± 10.8	23.6 ± 9.7	0.58
	Paired t	**0.010** (↓17.4%)**	**0.003** (↓18.3%)**	

p<0.05*, p<0.01**, p<0.001***

FIG 4.66: IMPACT OF TINOSPORA CORDIFOLIA SUPPLEMENTATION ON PREVALENCE OF DYSLIPIDEMIA IN TYPE 2 DIABETICS WITH DYSLIPIDEMIA (%)

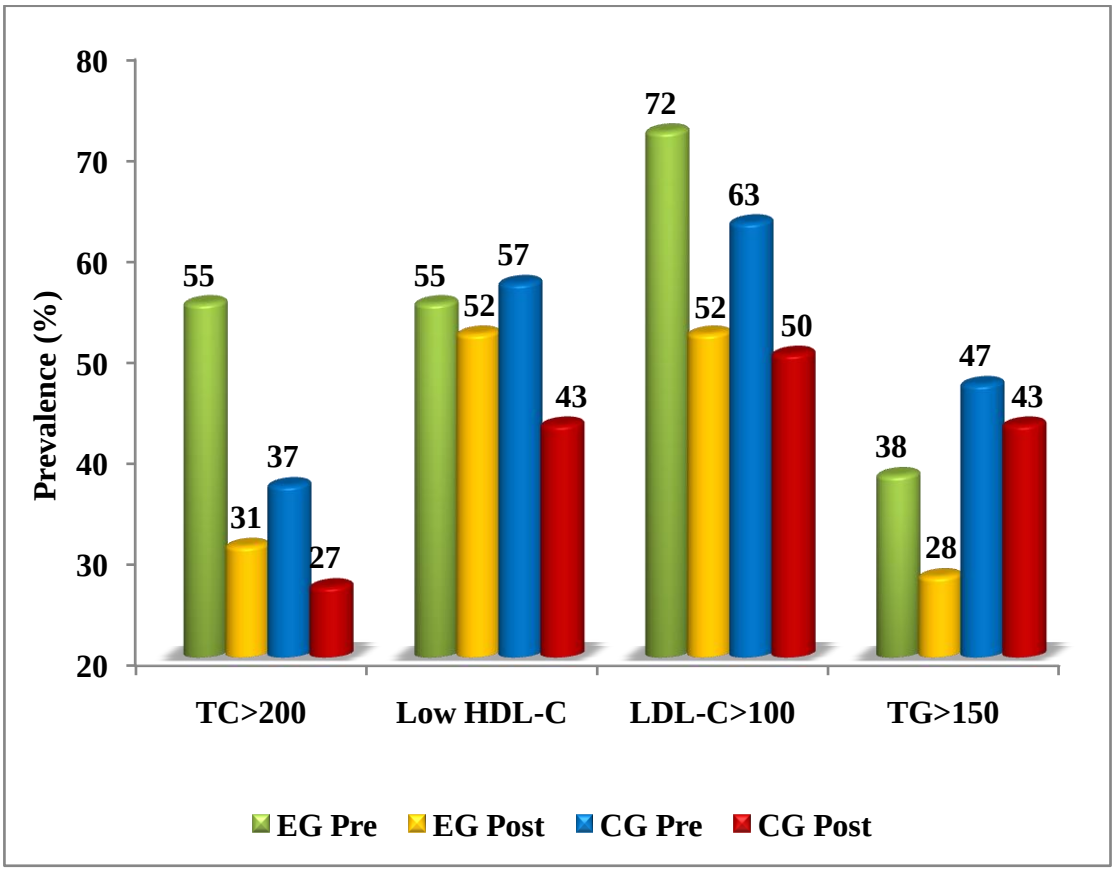


TABLE 4.122: IMPACT OF TINOSPORA CORDIFOLIA SUPPLEMENTATION ON NUMBER OF DYSLIPIDEMIC FEATURES IN TYPE 2 DIABETICS WITH DYSLIPIDEMIA (MEAN ± SD)

Variables	Stage	Control Group (N=30)	Experimental Group (N=29)	P value
Avg no. of dyslipidemic features	Pre	2.06 ± 1.11	2.27 ± 1.27	0.50
	Post	1.66 ± 0.99	1.62 ± 1.17	0.87
	Paired t	**0.020* (↓19.4%)**	**0.0036** (↓28.6%)**	

p<0.05*, p<0.01**, p<0.001***

TABLE 4.123: IMPACT OF TINOSPORA CORDIFOLIA SUPPLEMENTATION ON LIPID RATIOS OF TYPE 2 DIABETICS WITH DYSLIPIDEMIA (MEAN ± SD, N, %)

Variables	Stage	Control Group (N=30)	Experimental Group (N=29)	P Value
TG/H	Pre	3.5 ± 1.5	3.6 ± 2.6	0.92
	Post	3.0 ± 1.3	2.9 ± 1.5	0.98
	Paired t	**0.0014** (↓14.3%)**	0.07 (↓19.4%)	
TG/H >3	Pre	19 (63.3)	12 (41.4)	0.09
	Post	14 (46.7)	11 (37.9)	0.50
	χ^2	0.19	0.79	
AIP	Pre	0.49 ± 0.22	0.46 ± 0.26	0.61
	Post	0.42 ± 0.23	0.42 ± 0.41	0.98
	Paired t	**0.0009*** (↓14.3%)**	0.19 (↓8.7%)	
AIP >0.21	Pre	26 (86.7)	25 (86.2)	1
	Post	24 (80)	23 (79.3)	0.94
	χ^2	0.49	0.49	
TC/HDL	Pre	4.24 ± 0.83	4.78 ± 1.58	0.11
	Post	3.85 ± 0.87	4.08 ± 1.3	0.45
	Paired t	**0.018* (↓9.2%)**	**0.0002*** (↓14.6%)**	
TC/HDL>5	Pre	8 (26.6)	11 (37.9)	0.35
	Post	2 (6.6)	6 (20.6)	0.14
	χ^2	**0.039***	0.15	
LDL/HDL	Pre	2.54 ± 0.78	2.81 ± 1.09	0.28
	Post	2.2 ± 0.68	2.4 ± 0.86	0.25
	Paired t	**0.002** (↓13.4%)**	**0.0019** (↓14.6%)**	
LDL/HDL >3.5	Pre	4 (13.3)	5 (17.2)	0.73
	Post	1 (3.3)	4 (13.7)	0.19
	χ^2	0.35	1	

p<0.05*, p<0.01**, p<0.001***, values in parenthesis indicate percentage

Impact on Hs-CRP Status

Hs-CRP declined significantly with the intervention (4.6 to 2.8mg/l, P 0.0007) (table 4.124). The prevalence of low risk CVD (<1mg/l hs-CRP), declined in the control arm (26.6% to 23.3%) and increased in the experimental arm after the intervention (6.9% to 10.3%). The prevalence of high risk CVD declined by 13.4% in the control arm and by 27.6% in the experimental arm (65.5% to 37.9%, P 0.03) after the intervention (fig 4.67).

Impact on Thyroid Profile

No alterations were observed in the thyroid profile between and within groups. Only T3 declined significantly by 6.1% (100.7ng/dl to 94.6ng/dl) in the experimental arm after the intervention (P 0.027).

Impact on Hepatic Profile

At baseline all the parameters were similar between both the groups. Alkaline phosphatase declined significantly in the experimental arm after the intervention by 11.4% (96.2U/L to 85.2 U/L, P 0.0013). Bilirubin total (P 0.021) and bilirubin indirect (P 0.047) increased significantly only in the control arm. SGPT, SGOT and GGT reduced non-significantly in the intervention arm. Total protein declined significantly by 2.7% in the intervention arm (7.3g/dl to 7.1g/dl, P 0.011) and by 5.3% among controls (7.5g/dl to 7.1g/dl, P 0.0016), however, remained in the normal range (table 4.125).

Impact on Glycemic Profile

HbA1c and ABG were similar at baseline in both the arms and had a non-significant decline post intervention. However, the decline was more evident in the experimental arm (by 2.6%, 7.7% to 7.5%, P 0.09) than the control arm (by 1.1%, 7.9% to 7.81%, P 0.52) (table 4.126). The prevalence of normoglycemia (HbA1c <6%) shot up in the experimental arm (6.8% to 10.3%) after the intervention. However, the prevalence of good glycemia (HbA1c 6-7%) remained static in both the arms pre and post intervention. The prevalence of HbA1c >8% declined in both the arms after the intervention with drop more evident in the control arm (46.6% to 36.6%) than the experimental arm (34.4% to 27.5%) (fig 4.68).

TABLE 4.124: IMPACT OF TINOSPORA CORDIFOLIA SUPPLEMENTATION ON Hs-CRP OF TYPE 2 DIABETICS WITH DYSLIPIDEMIA (MEAN ± SD)

	Stage	Control Group (N=30)	Experimental Group (N=29)	P value
Hs-CRP (mg/l)	Pre	4.3 ± 3.5	4.6 ± 3.2	0.72
	Post	3.4 ± 3.6	2.8 ± 2.4	0.44
	Paired t	0.10 (↓20.9%)	**0.0007*** (↓39.1%)**	

p<0.05*, p<0.01**, p<0.001***

FIG 4.67: IMPACT OF TINOSPORA CORDIFOLIA SUPPLEMENTATION ON PREVALENCE OF ELEVATED Hs-CRP OF TYPE 2 DIABETICS WITH DYSLIPIDEMIA (%)

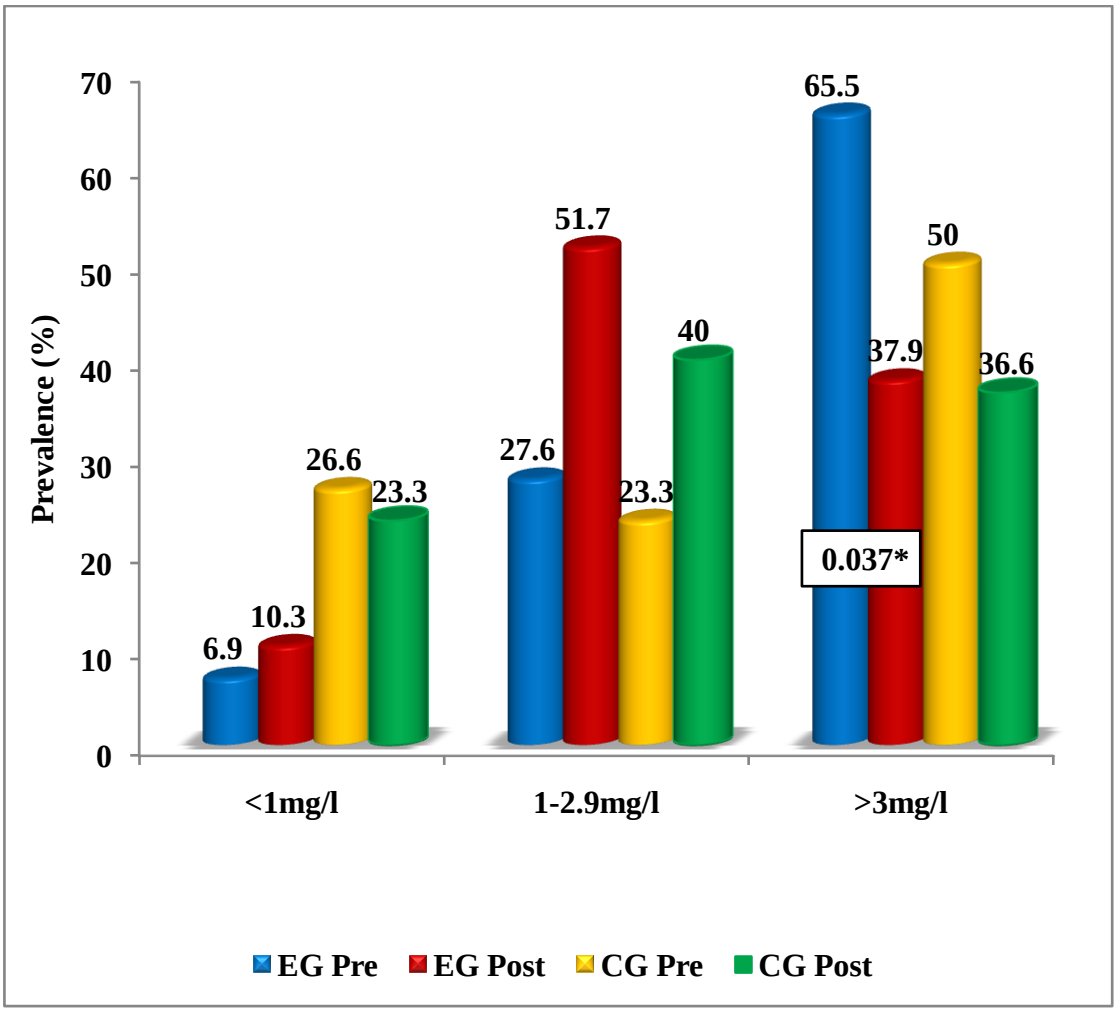


TABLE 4.125: IMPACT OF TINOSPORA CORDIFOLIA SUPPLEMENTATION ON HEPATIC PROFILE OF TYPE 2 DIABETICS WITH DYSLIPIDEMIA (MEAN ± SD)

Variables	Stage	Control Group (N=30)	Experimental Group (N=29)	P Value
Alkaline phosphatase (U/L)	Pre	89.2 ± 26.1	96.2 ± 15.7	0.22
	Post	86.5 ± 24.3	85.2 ± 17.1	0.82
	Paired t	0.24 (↓3%)	**0.0013** (↓11.4%)**	
Bilirubin direct (mg/dl)	Pre	0.19 ± 0.06	0.18 ± 0.05	0.51
	Post	0.19 ± 0.06	0.18 ± 0.05	0.51
	Paired t	0.77 (0%)	0.83 (0%)	
Bilirubin total (mg/dl)	Pre	0.65 ± 0.21	0.62 ± 0.21	0.63
	Post	0.72 ± 0.29	0.60 ± 0.20	0.08
	Paired t	**0.021* (↑10.7%)**	0.63 (↓3.2%)	
Bilirubin indirect (mg/dl)	Pre	0.45 ± 0.15	0.44 ± 0.15	0.78
	Post	0.52 ± 0.25	0.42 ± 0.14	0.07
	Paired t	**0.047* (↑15.5%)**	0.48 (↓4.5%)	
GGT (U/L)	Pre	25.1 ± 13.6	26.3 ± 11.2	0.74
	Post	25.1 ± 12.7	24.1 ± 10.3	0.75
	Paired t	0.99 (0%)	0.22 (↓8.4%)	
SGOT (U/L)	Pre	20.8 ± 8.5	23.2 ± 11.1	0.35
	Post	19.6 ± 5.9	23.08 ± 11.05	0.16
	Paired t	0.2 (↓5.7%)	0.93 (↓0.51%)	
SGPT (U/L)	Pre	23.3 ± 13.2	28.1 ± 15	0.19
	Post	22.3 ± 7.6	25.9 ± 14.1	0.22
	Paired t	0.53 (↓4.3%)	0.36 (↓7.8%)	
Total protein (g/dl)	Pre	7.5 ± 0.5	7.3 ± 0.4	0.50
	Post	7.1 ± 0.34	7.1 ± 0.41	0.79
	Paired t	**0.0016** (↓5.3%)**	**0.011* (↓2.7%)**	
Albumin (g/dl)	Pre	4.2 ± 0.2	4.2 ± 0.3	0.64
	Post	4.2 ± 0.23	4.19 ± 0.18	0.78
	Paired t	0.53 (0%)	0.84 (↓0.23%)	

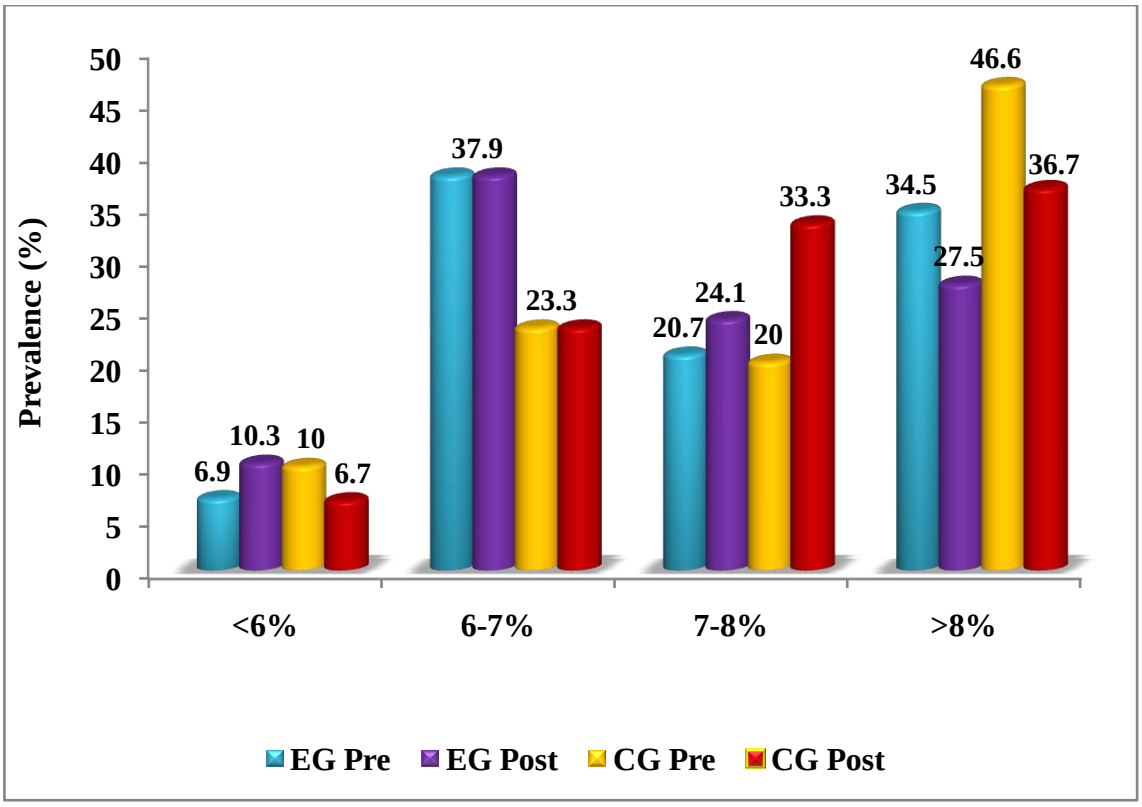
$p<0.05$*, $p<0.01$**, $p<0.001$***

TABLE 4.126: IMPACT OF TINOSPORA CORDIFOLIA SUPPLEMENTATION ON GLYCEMIC PROFILE OF TYPE 2 DIABETICS WITH DYSLIPIDEMIA (MEAN ± SD)

Variables	Stage	Control Group (N=30)	Experimental Group (N=29)	P Value
HbA1c (%)	Pre	7.9 ± 1.7	7.7 ± 1.5	0.55
	Post	7.81 ± 1.69	7.5 ± 1.5	0.50
	Paired t	0.52 (↓1.1%)	0.09 (↓2.6%)	
ABG (mg/dl)	Pre	181.2 ± 53.5	176.2 ± 44.9	0.57
	Post	176.9 ± 49.6	168.6 ± 46.5	0.51
	Paired t	0.51 (↓2.4%)	0.06 (↓4.3%)	

p<0.05*, p<0.01**, p<0.001***

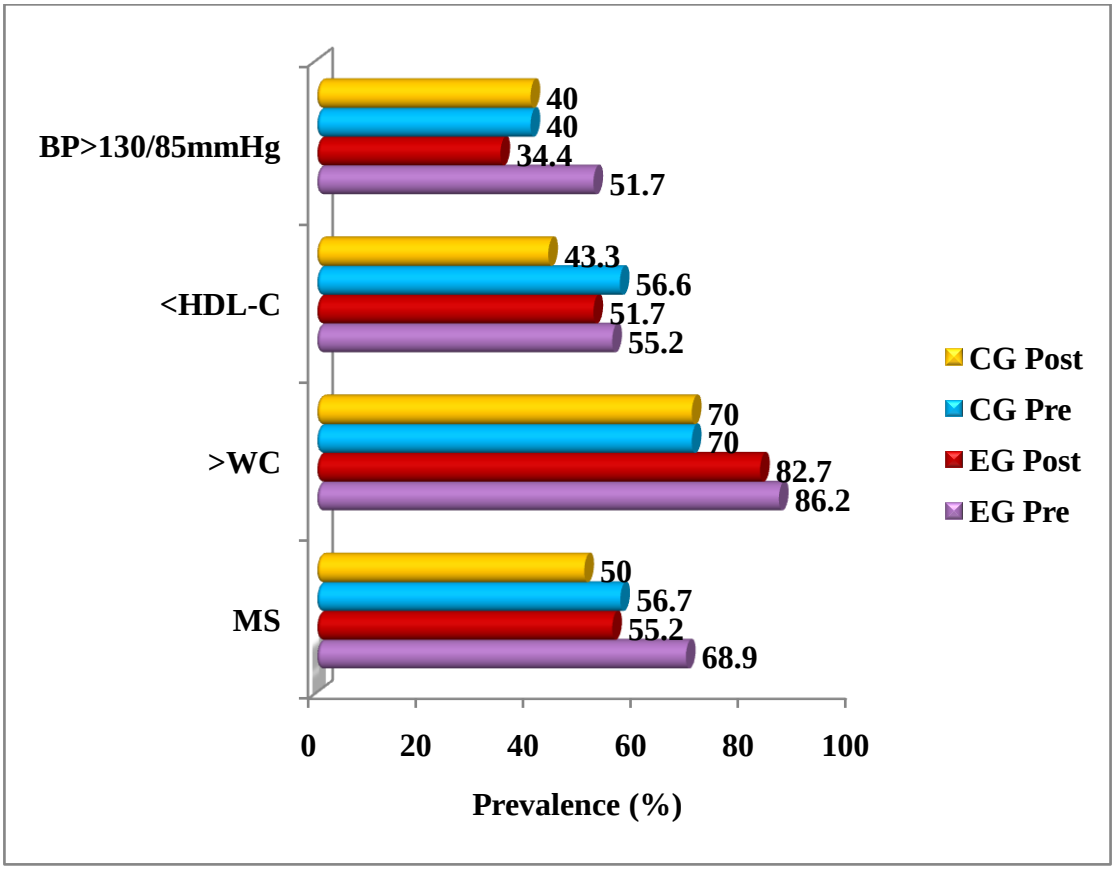
FIG 4.68: IMPACT OF TINOSPORA CORDIFOLIA SUPPLEMENTATION ON HbA1c STATUS OF TYPE 2 DIABETICS WITH DYSLIPIDEMIA (%)



Impact on Prevalence of Metabolic Syndrome

According to the IDF classification for defining MS, the prevalence at baseline was non-significantly higher among the intervention arm subjects than the controls (68.9% vs. 56.7%, P 0.33). However, the intervention reduced the prevalence of MS by 13.73% (68.9% to 55.17%) in the intervention subjects and by only 6.7% (56.7% to 50%) in controls. The number of features of MS came down from 3.2 to 2.86 (P 0.059) in the intervention arm subjects, with maximum changes being evident in reduction in blood pressure and improvement in triglycerides and only a minor change occurred in controls (3.13 to 3.06, P 0.62). Importantly, prevalence of abdominal obesity declined only among the intervention subjects whereas that of controls remained unaltered (fig 4.69).

FIG 4.69: IMPACT OF TINOSPORA CORDIFOLIA SUPPLEMENTATION ON PREVALENCE OF METABOLIC SYNDROME (IDF) IN TYPE 2 DIABETICS WITH DYSLIPIDEMIA (%)



DISCUSSION

Dyslipidemia in type 2 diabetics is the root cause of macrovascular complications namely, CVD, cerebrovascular disease and peripheral vascular disease (Farmer, 2008). Although it is a modifiable risk factor for CVD (Saydah et al., 2004), it accounts for 70% of all deaths in this population (Kershnar et al., 2006). Therefore, management of diabetic dyslipidemia warrants attention (ADA, 2003). Statin (3-hydroxy-3-methylglutaryl coenzyme A reductase) is used as initial therapy (ADA, 2002) for lowering LDL-C level in patients with type 2 diabetes who either have overt CVD or are >40 years of age and have increased CVD risk (Goff et al., 2007). However, even with the statin therapy the risk of CVD lurks (Goff et al., 2007; Vijayaraghavan, 2010). Moreover, the desired impact of the drug is often marred by the side effects it confers (Stancu and Sima, 2001). This is where phyto-medicines score over the modern medicine as they are of natural origin, have lesser side effects, (Modak et al., 2007; Pandey et al., 2013) and better efficiency (Yadav and Agarwala, 2011; Pandey et al., 2013; Konda et al., 2013).

A medicinal plant with anti-diabetic and anti-dyslipidemic potential is Tinospora cordifolia. It belongs to the family *Menispermaceae* (Sankhala et al., 2012) and is a rich source of alkaloid and terpenes (Sharma et al., 2010). The stem is highly nutritive, digestive (Sinha et al., 2004) and contains; berberine, palmatine, tembetarine, magnoflorine, tinosporin, tinocordifolin (Kumar et al., 2000; Maurya et al., 1997). The stem is approved for medicinal usage (MOHFW, 2001).

The stem extract has demonstrated antidyslipidemic activity in alloxan-induced diabetic rats (Mahdi et al., 2013) and streptozotocin-induced diabetic rats (Nagaraja et al., 2008), anti-diabetic activity in streptozotocin diabetic rats (Rajalakshmi et al., 2009), streptozotocin diabetic albino rats (Puranik et al., 2010). Another study on diabetes induced Wistar rats demonstrated that alcoholic stem extract of tinospora cordifolia has antidiabetic and antihyperlipidemic potential (Selvaraj et al., 2012). It has shown to be a better drug to regress diabetic-dyslipidemia (Mahdi et al., 2013) and the extrapancreatic and intrapancreatic activities are postulated to impart the anti-diabetic effect (Sharma et al., 2015).

With no clinical studies after showing commendable impact on the glycemic and lipemic profile in animal models, the stem may hold potential to manage dyslipidemia and dysglycemia in type 2 diabetics. Thus, the study was designed to study the impact of tinospora cordifolia stem supplementation on subjects with diabetic dyslipidemia. Type 2 diabetics on oral hypoglycemic agents and statin were enrolled from a diabetic clinic. They were randomly assigned into two groups, experimental arm (n=29) that received tinospora cordifolia stem capsules (250 mg twice daily pre meal) along with statin and OHAs and control arm received statin and OHAs for duration of 60 days.

Qualitative Phytochemical Profile

The given sample of tinospora cordifolia may impart anti-diabetic effect because of the presence of alkaloids, tannins, cardiac glycosides and flavonoids present in the stem (Zinjarde et al., 2011). The presence of tannins determines that tinospora cordifolia maybe interfering with protein synthesis by binding to proline rich protein (Marjorie, 1996). Qualitative phytochemical screening of tinospora cordifolia also found the presence of alkaloids. Thus, alkaloids may be imparting analgesic effect (Nasreen et al., 2010), antispasmodic, antibacterial (Okwu, 2004), anti-inflammatory and anti-oxidant (Nasreen et al., 2010) properties as well. The presence of flavonoids confirms antioxidant activity in the given sample of tinospora cordifolia. It may either act as chain breaking antioxidant or suppress lipid peroxidation by recycling the antioxidants (McAnlis et al., 1999). Tinospora cordifolia may also be acting as an anti-microbial agent owing to the presence of flavonoids (Marjorie, 1996). Terpenoids are known to act as anti-bacterials, anti-neoplastic and the presence of the terpenoids confirms the above mentioned biological activities in the given sample (Nasreen et al., 2010). Anti-inflammatory activity of the given sample is further confirmed by the presence of cardiac glycosides.

Impact of Tinospora Cordifolia Stem Supplementation

The supplementation demonstrated anti-inflammatory role of tinospora cordifolia stem as the hs-CRP and uric acid declined significantly and also significantly brought down the prevalence of high risk CVD. Anti-inflammatory activity (Shah et al., 2011) of the given sample is further confirmed by the presence of cardiac glycosides

(Matsumori et al., 1997). The alkaloids present in the stem are also known to impart anti-inflammatory and anti-oxidant effect (Nasreen et al., 2010).

Though statistically non-significant, drop in HbA1c and ABG was greater in the experimental arm. This explains the possible anti-diabetic function of tinospora cordifolia stem because of the presence of alkaloids (Magnoflorine, Palmetine, Jatrorrhizine) (Patel and Mishra, 2011), tannins, cardiac glycosides, saponins, steroids and flavonoids (Zinjarde et al., 2011; Sudha et al., 2011), wherein the biological mechanism postulated is promotion of insulin secretion by inhibiting gluconeogenesis and glycogenolysis by the stem (Patel and Mishra, 2011). Its extrapancreatic activities such as glycogenesis/inhibited glycogenolysis in liver, improving glucose uptake and utilization, inhibiting gluconeogenesis, inhibiting intestinal glucose absorption, inhibiting α-glucoside and α-amylase, mitigating oxidative stress, antioxidant properties and protection against tissue damage, seem to contribute profoundly to diabetes. The intrapancreatic actions involve preventing and restoring integrity and functioning of β cells, promoting endogenous insulin secretion/insulinotropic action and reduction of IR (Sharma et al., 2015).

Further evidence comes from a study wherein hexane, ethyl acetate and methanol Tinospora cordifolia stem extract at a dose of 250 mg/kg b.w. for a period of 100 days had an antidiabetic effect which reduced blood sugar level in streptozotocin induced diabetic rats. The supplementation also significantly reversed reduced glucokinase and increased glucose-6-phoaphatase activity and decreased the HbA1c (Rajalakshmi et al., 2009).

Streptozotocin diabetic albino rats benefited from different dosages (200 and 400 mg/kg b.w.) of tinospora cordifolia stem extracts (both aqueous and alcoholic) as it had significant anti-diabetic activity in diabetic animals and had an efficacy of 40% to 80% compared to insulin (Puranik et al., 2010). Because the extract did not cause any increase in serum insulin levels or regeneration of pancreatic β cells but caused increased hepatic glycogen synthase and decreased glycogen phosphorylase activity, it was postulated by the authors that tinospora cordifolia maybe acting as an anti-hyperglycemic drug through some peripheral mechanisms, such as increasing the glycogen storage in the liver or by decreasing the activity of glycogen phosphorylase, thereby retarding or preventing glucose release from the liver (Puranik et al., 2010).

Solvent extracted tinospora cordifolia stems, especially water, ethanol and methanol extracts showed glucose uptake activity through glucose transporters, 1 (GLUT1) and 3 (GLUT3) in Ehrlich ascites tumor (EAT) cells (Darukeshwara et al., 2014).

Advantageously, tinospora cordifolia administration along with metformin has shown beneficial pharmacokinetic and pharmacodynamic interaction leading to enhancing antihyperglycemic and antihyperlipidemic activities (Patwardhan, 2012). Infact, berberine, the alkaloid present in the stem has shown to boost the effects of metformin and 2,4-thiazolidinedione (Prabhakar and Doble, 2009) and is known to lower elevated blood glucose as effectively as metformin (Sharma and Batra, 2013). This could be one of the possible reasons why the intervention arm subjects had a more evident anti-diabetic profile than the controls, although a higher dosage or a longer duration of the trial could have brought about significant changes in the glycemic profile. Tinospora cordifolia stem extract has also been found to inhibit the salivary, pancreatic amylase and alpha glucosidase in a non-competitive manner (Arvindekar et al., 2009). Of the alkaloids, magnoflorine possesses the most potential activity as α-glucosidase inhibitor in vitro and in vivo (Patel and Mishra, 2011). This may hold potential for the extract to be used in postprandial hyperglycemia control.

Total cholesterol reduced more prominently with the intervention. The stem is also known to contain saponins which might have bound cholesterol in the present study (Okwu, 2004). Berberine by adenosine monophosphate-activated protein kinase activation is also known to decrease the cholesterol level (Sharma and Batra, 2013). The average number of features of dyslipidemia reduced significantly with tinospora cordifolia stem supplementation. To support that, the stem extract has shown to normalize lipid metabolism alterations caused by diabetes mellitus in streptozotocin-induced diabetic rats (Nagaraja et al., 2008). The extracts may not have the similar mechanism of action by interfering HMG-CoA reductase and may be due to the interference of cholesterol with residues at the absorption site in gastro-intestinal tract (GIT) since they were co-administered. There was a significant decrease in lipids and HDL-C remained unaffected in Sprague dawley rats that were induced with hyperlipidemia but were treated with methanolic extract of tinospora cordifolia stem at 400 mg kg-1 dose. The reduction was found to be significant when compared with atorvastatin, though of lesser intensity (Thahera and Nyamathulla, 2011).

The antidyslipidemic activity of tinospora cordifolia stem extract has been demonstrated in alloxan-induced (150 mg/kg body wt.) diabetic rats who were (dyslipidemic) orally fed stem extract (500 mg/kg body weight) for 15 days that resulted in significant decrease in plasma glucose, HbA1c lipid peroxide, total lipid and FFA. The extract also had an anti-diabetic effect but it was lesser in intensity than glibenclamide. Antidiabetic and antidyslipidemic activities of tinospora cordifolia stem may be partly due to presence of the alkaloids (Mahdi et al., 2013). A significant effect on gluconeogenic enzymes glucose-6- phosphatase and fructose 1, 6-bisphosphatase activity in streptozotocin induced diabetic albino rats was observed following the administration of aqueous and alcoholic stem extracts at 200 and 400 mg/ kg b.w (Puranik et al., 2007).

Another study on diabetes induced Wistar rats demonstrated that alcoholic stem extract of tinospora cordifolia has antidiabetic and antihyperlipidemic potential (Selvaraj et al., 2012). Evidence of antidyslipidemic activity of the tinospora cordifolia stem extract comes from a study on alloxan induced diabetic rats who were orally administered 500 mg/kg bw stem extract for 30 days, blood glucose, plasma lipids reduced significantly and post heparin lipoprotein lipase activity was reactivated. Importantly, the extract inhibited the generation of super oxide anions and hydroxyl radicals, in both enzymic and non-enzymic systems in vitro (Kumar, 2015).

Metabolic syndrome reduced more prominently in supplementation group than the controls. This could have been possibly due to two reasons. One, anti-hypertensive role of tinospora cordifolia was evident as it brought down the SBP more prominently than the controls, who had a similar anti-hypertensive drug profile. Secondly, elevated waist circumference was the most common feature of the metabolic syndrome in the present study and the supplementation brought down the mean waist circumference. These two factors in congregation must have reduced the prevalence of MS more prominently in the intervention arm than the controls. A reduction in the lipid profile together with reduction in the prevalence of metabolic syndrome signifies reduced risk of adverse cardiac events. Berberine has been documented to improve hepatic metabolism during IR and MS and by adenosine monophosphate-activated protein kinase activation maintains the blood pressure (Sharma and Batra, 2013).

This is the first trial to document the impact of tinospora cordifolia stem in the management of diabetic dyslipidemia and dysglycemia. As the drug, diet and physical activity profile was similar in both the arms; the added effect in the experimental arm can be attributed to the tinospora cordifolia stem supplementation *per se*. The compliance in the study was assumed to be 100% as empty tablet containers were returned on completion of the study period. As no adverse effects were reported in the subjects, other than a single drop out reporting lower GIT disturbance, the dosage was within the tolerable limits. This is further corroborated as the surrogate laboratory safety biomarkers remained within the normal limit. Having the benefit of being desirable as a supportive glycemic drug (Sharma et al., 2015; Puranik et al., 2010) and known to boost the effect of OHAs (Prabhakar and Doble, 2009), tinospora cordifolia stem supplementation can be an adjunct therapy to deal with the dual problems of dyslipidemia and dysglycemia. However, the study had certain limitations to it. It had a relatively smaller sample size and was of shorter duration.

CONCLUSIONS

A dose of 500 mg tinospora cordifolia stem over a two months period brought about more evident changes in the lipoprotein fractions, HbA1c, inflammatory markers and metabolic syndrome. With no major or minor adverse events reported, it only sets ground for conduction of aggressive clinical trials to further validate the first set of findings on the impact of tinospora cordifolia stem in the management of dyslipidemia and dysglycemia in patients with type 2 diabetes.