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Protective Effect of *Lagenaria siceraria* (Mol.) Standl. Against Carbamezapine Induced Hyperlipidemia: Comparative Study Between Male And Female Animal Model

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ABSTRACT

The present investigation focuses the use of *Lagenaria siceraria* in reduction of Carbamezapine induced hyperlipidemia. LSFJ and CBZ were given orally for 90 days to both genders and blood sample were analyses for lipid profile. Significantly high values of cholesterol were observed in both genders of rabbits treated with CBZ, whereas high values of LDL and high value of HDL were observed in male and female rabbits respectively. The LSFJ showed increased HDL and decreased in total cholesterol and triglycerides (P<0.0001) in both genders. Concurrent administration of LSFJ with CBZ showed increased HDL and decreased LDL and triglycerides in female subjects whereas decreased triglycerides were observed in males.

These results shows that CBZ induced hyperlipedimia were more significant in females which may leads to high risk of atherosclerosis. The adjuvant therapy of LSFJ may be considered to lower the hyperlipedimia accociated with chronic treatment with antiepileptic drugs.

Keywords: Anti-hyperlipidimic, carbamezapine, *Lagenaria. Siceraria,* obesity

INTRODUCTION

A lifelong therapy is required in epileptic patient, a prolonged treatment has some unwanted effects. Several reports have already showed that an antiepileptic drugs (AEDs) increased cholesterol and lipoprotein in serum. There is an increased risk of atherosclerosis associated with high serum level of cholesterol and lipoproteins [1].

Thereforea careful monitoring of serum lipid profile and a lipid lowering diet is necessary in patients taking carbamezapine for long term therapy.

Lagenaria siceraria (Mol.)fruit known as bottle gourd or lauki, used as a food in Pakistan. It has cardioprotective, general tonic and diuretic properties which may be due to the presence of its phytochemicals included alkaloids, cardiac glycoside, saponins, tannins, flavinoids and phytosterols [2]. Traditionally this fruit along seeds is used without epicarp and found to be a good source of choline, vitamin B complex, fibers, and proteins [3]. Literature also reported that *L.siceraria*have more soluble dietary fibers (SDF) than insoluble cellulose fibers (ICF), SDF have property to lowers the cholesterol due to the pectin as a component in SDF of *L. siceraria* fruits [4].

A few prospective studies with the increased in lipid profile associated with antiepileptic drugs (mainly carbamezapine, phenytoin, and Phenobarbital) with gender related differences of serum lipid levels have been evaluated. Hindi *et al.,* found a significant increased in LDL-C in females, whereas, Calandre *et al*., only observed an increased in males. Isojarvi *et al.,* and Sudhop *et al.,* found significantly higher LDL-C concentrations in both sexes compared with a control group[5-8].

MATERIAL AND METHOD:

Animal

Healthy adult rabbits of a local strain (*Oryctolagus cuniculus*) with an initial weight of 1 kg were housed in stainless cages under standard laboratory condition (light period: 8:00 am to 8:00 pm, 21±2°C, relative humidity 55%, green fodder and water were available ad libitum), at animal house of Dow University of Health Sciences, Karachi.

Rabbits were divided into eight groups (n=8),

Group I: Control Male

Group II : Control Female

Group I – A: Treated with Carbamezapine (CBZ)

Group I – B: Treated with *Lagenaria siceraria* Fruit Juice (LSFJ).

Group I – C: Treated with combination of Carbamezapine and *Lagenaria siceraria* Fruit Juice (CBZ + LSFJ).

Group II – A: Treated with Carbamezapine (CBZ)

Group II – B: Treated with *Lagenaria siceraria* Fruit Juice (LSFJ).

Group II – C: Treated with combination of Carbamezapine and *Lagenaria siceraria* Fruit Juice (CBZ + LSFJ).

Dose

Drug was administrated orally for 90 days at interval of 24 hr at dose of carbamezapine 6 mg/ml and fresh juice of whole fruit of *L.siceraria* was given at dose of 3.5 ml (240mg/kg). Physical behavior and signs of any sort of illness were observed daily.

The initial weights of rabbits of all groups were around 1-1.3 kg before treatment. During experimental period, food consumed and weight gained by rabbits were recorded on 1st month, 2nd month and 3rd month of carbamezapine (CBZ) and combination of carbamezapine and *L. siceraria* (Mol.) (CBZ + LSFJ).

Biochemical studies

For biochemical analysis, blood was collected directly from heart by cardiac puncture 10ml blood was dispensed into plain bottles, allowed to clot and centrifuged at 3500 rpm for 10 min. The clear sera aspirated off for biochemical evaluation viz; total cholesterol, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), very low density cholesterol (VLDL-C) and triglycerides (TG) using commercial kits obtained from Randox Laboratories, UK [9].

Statistical analysis

ANOVA is applied on the data, subjected to one way analysis of variance for comparison among different groups. $p>0.005$ was considered as non-significant whereas, $p<0.005$ and $p<0.0001$ was considered as significant and highly significant values respectively. Values were expressed as mean ± SEM (n=5).

RESULTS AND DISCUSSION

After 90 days of successful administration of drug, following results were obtained. In male and female rabbits, when treated with CBZ, 78% and 113% weight gained was observed respectively as compared with control. LSFJ treated group reduced weight 57% and 76% in comparision with carbamezapine in male and female respectively. Group treated with LSFJ + CBZ, reduced weight observed was 75% in male and 85% in female in comparision with carbamezapine group. LSFJ may effective in obesity as well as maintain weight in longer use.

Table 1 shows the effect of CBZ and LSFJ and combination of both drugs. The cholesterol value with CBZ treated group was highly increased as compared to control group(C=19 ± 1.22, CBZ=187 ± 0.63) with $p<0.0001$.In combination with CBZ +LSFJit gave a highly significant results $p<0.0001$ (CBZ=187 ± 0.63, CBZ+ *L. siceraria*=31 ± 0.71) decreased the value of total cholesterol in male rabbits. The level of triglycerides, HDL, LDL, and VLDL were significant high

values in carbamezapine group I-A (Table 1). Where as a combination of CBZ + LSFJ reduced triglycerides, HDL, LDL, and VLDL value significantly. LSFJ shows its anti-hyperlipidimic effect with significant values (Table 1).

Lipid profile of Group II (female) treated with carbamezapine and LSFJ were compared with control, it showed that carbamezapine significantly increased the value of cholesterol, triglycerides, HDL, LDL and VLDL (p<0.0001). LSFJdid not show change in total cholesterol (p>0.005) however it significantly reduced HDL, LDL, VLDL (P<0.005) and triglycerides (P<0.0001). Results of Group II-C (CBZ + LSFJ) showed highly significant reduction in total cholesterol, LDL, triglycerides, HDL and VLDL (Table 2, figure 3a-c).

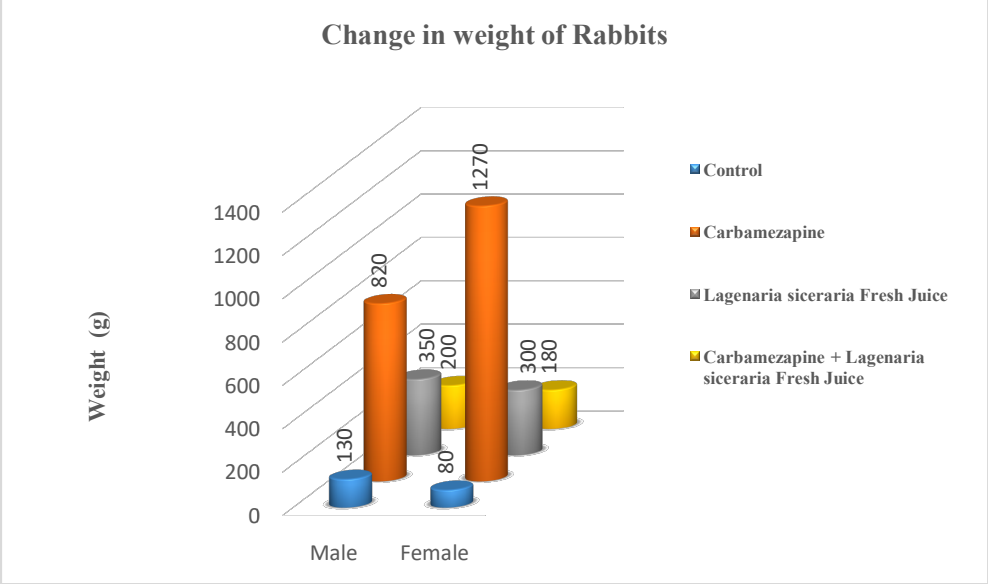


Figure 1: Effects on body weight in gram during treatment

Table 1 - Lipid lowering effect of *Lagenaria siceraria* with Anti-epileptic drug Carbamezapine on lipid profile of male rabbits

	Cholesterol HDL Ratio	Cholesterol	Triglycerides	HDL	LDL	VLDL
Group I (Control)	3.18 ± 0.08	19 ± 1.22	110 ± 1.67	6 ± 0.32	12 ± 0.32	22 ± 0.71
Group I – A (Carbamezapine)	9.8 ± 0.07^{HS}	187 ± 0.63^{HS}	141 ± 0.45^{S}	19 ± 0.32^{HS}	148 ± 0.71^{HS}	28 ± 0.71^{S}
Group I – B (LSFJ)	3.5 ± 0.94^{NS}	39 ± 2.50^{HS}	64.2 ± 1.16^{HS}	11.4 ± 0.51^{HS}	24 ± 1.30^{HS}	13.2 ± 0.66^{HS}
Group I – C (Carbamezapine + LSFJ)	2.2 ± 0.19+-^{HS}	31 ± 0.71^{HS}	95 ± 2.00^{HS}	14 ± 1.14^{NS}	12 ± 0.71	19 ± 0.71^{NS}

Values are expressed as mg/dl (Mean ± SEM)(n=5)
Results of groups treated with carbamazepine and LSFJ are compared with control, whereas group given the combination of Carbamazepine and LSFJ are compared with the groups for the purpose of statistical analysis.
NS - p>0.005 ; S - p>0.005 ; HS - p<0.0001.

Table 3 - Lipid lowering effect of Lagenaria siceraria with Anti-epileptic drug Carbamezapine on lipid profile of female rabbits.

	Cholesterol HDL Ratio	Cholesterol	Triglycerides	HDL	LDL	VLDL
Group II (Control)	7 ± 0.51	78 ± 1.20	227 ± 11.35	11 ± 0.98	35 ± 2.51	45 ± 4.16
Group II – A (Carbamezapine)	9.7±0.34 ^{NS}	372± 3.47^{HS}	130± 6.19^{HS}	38± 2.73^{HS}	114± 4.79^{HS}	58 ± 2.12^{S}
Group II – B (LSFJ)	3.4±0.18^{HS}	80± 4.04^{NS}	58± 5.00^{HS}	23 ± 1.64^{S}	60± 4.78^{S}	23 ± 2.08^{S}
Group II – C (Carbamezapine + LSFJ)	2.2 ±0.15^{HS}	55± 4.27^{HS}	83± 3.39^{S}	25 ± 1.63^{S}	22± 1.89^{HS}	34 ± 3.17^{S}

Values are expressed as mg/dl (Mean ± SEM)(n=5)
Results of groups treated with carbamazepine and LSFJ are compared with control, whereas group given the combination of Carbamazepine and LSFJ are compared with the groups for the purpose of statistical analysis.
NS - p>0.005 ; S - p>0.005 ; HS - p<0.0001.

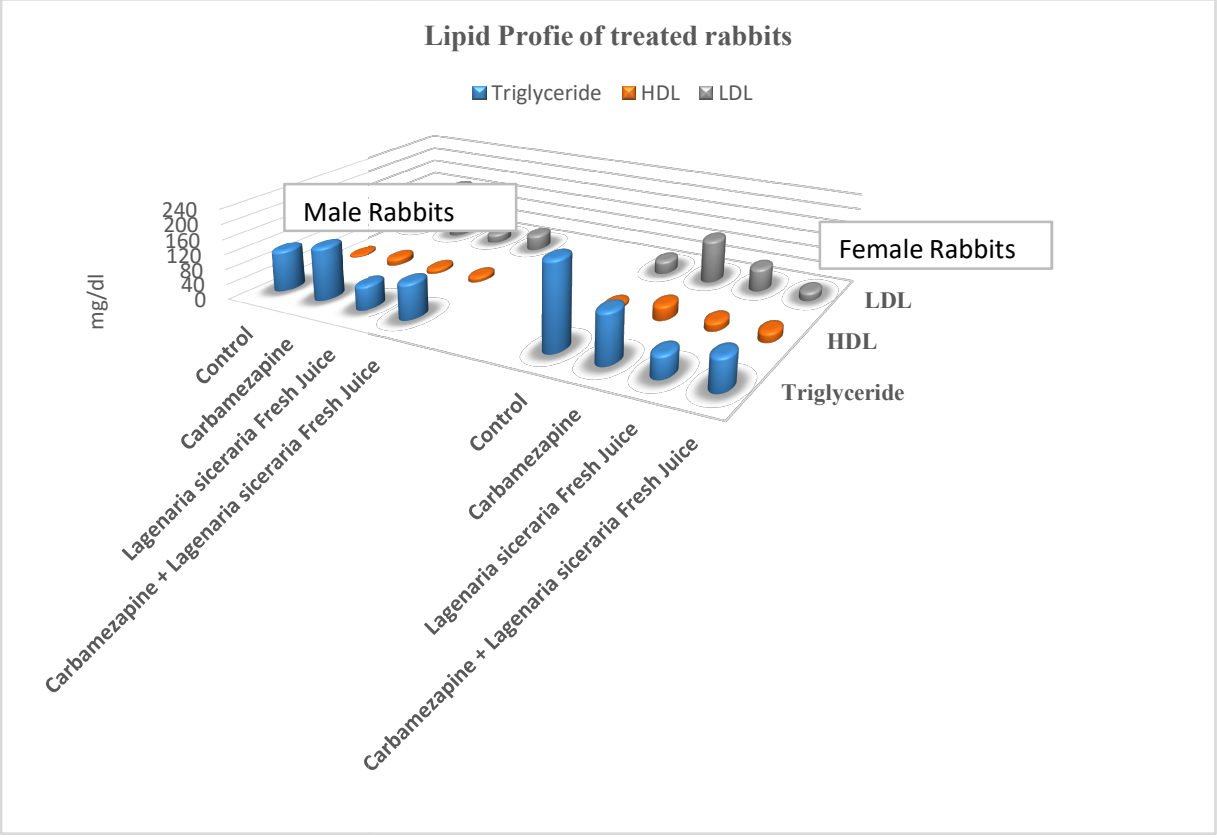


Figure 2: Graphical representation of lipid profile of male and female rabbits

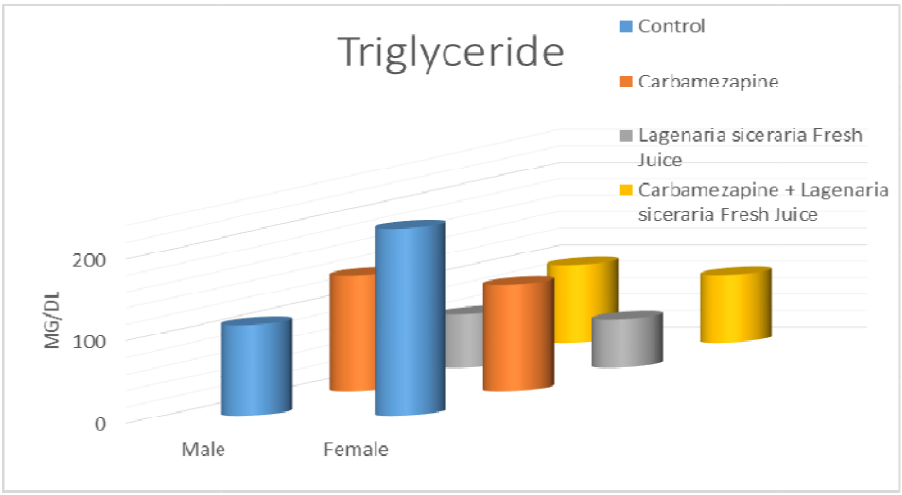
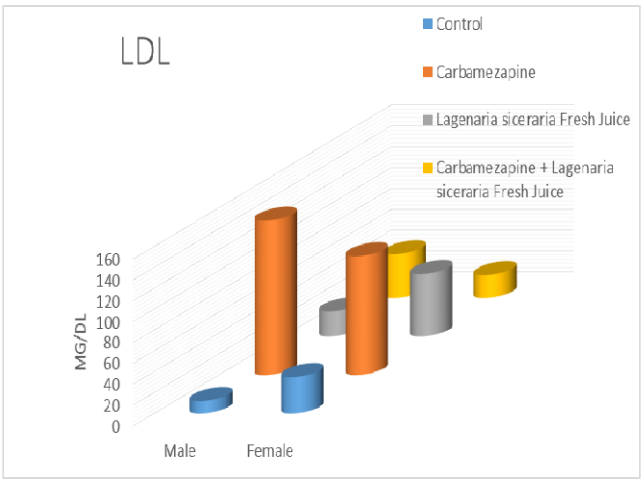


Figure 3a: Effect of CBZ, LSFJ and its combination on Triglycerides of Male and Female Rabbits



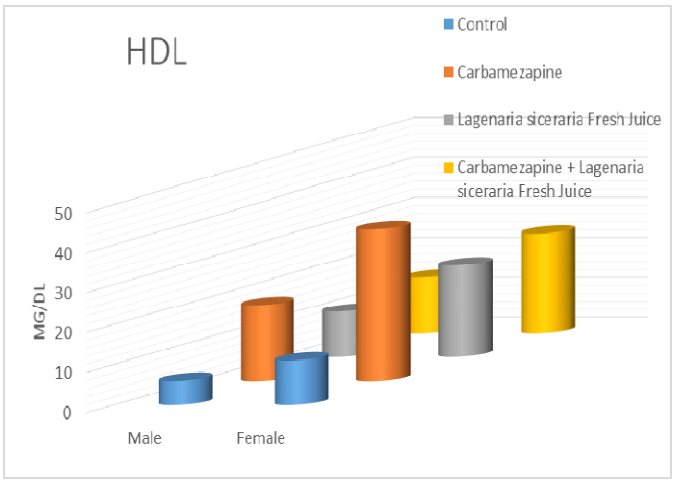


Figure 3b & 3c: Effect of CBZ, LSFJ and its combination on LDL and HDL of male and female Rabbits

In this animal study, carbamezapine treated group of male and female rabbit showed its effect on lipid profile through increased total cholesterol concentration in serum. As carbamezapine is P_{450}enzyme inducer, P_{450}microsomes metabolizes the carbamezapine, this enzyme also act on cholesterol and transformed it into biliary acids. Thus a long term use of carbamezapine may compete with cholesterol in utilizing of enzymes which blocks its transformation in bile acids and as a result of reduced biotransformation of cholesterol it increased the total serum cholesterol levels [10].

An increased in triglycer-rich lipoproteins is commonly associated with a reduction in HDL and an increase in small dense LDL levels. Hypertriglyceridemia stimulates the enzymatic activity of cholesteryl ester transfer protein (CETP), which facilitates the

transfer of TG from TG-rich lipoproteins to HDL and LDL in exchange for cholesteryl esters. This leads to an increased in TG content of HDL and LDL[11].The increased in LDL concentration in both male and female rabbits may be due to the increased HMG-CoA reductase activity, which reflects the activity of mevalonic acid, a endogenous cholesterol but a retrospective data on human showed that there was no change in endogenous cholesterol ratio, it is likely to be induce by P_{450} enzyme[8]. Thus over expression of the microsomal triglyceride transfer protein has been shown to increased VLDL-AP_{OB} and VLDL-triglyceride secretion in the liver[12]. With carbamezapine there were increased LDL and total cholesterol in epileptic patients. There is a significant decreased in LDL in female rabbits in combination (CBZ + LSFJ) which indicated its high potential towards antihyperlipidimic activity. This could be due to the saponins, constituent of fruit *L. siceraria* binds with cholesterol in intestinal lumen for its decreased absorption thus causing reduced extra hepatic circulation [13]. Pectin, a soluble dietary fiber is also one of the constituent of fruit *L. siceraria* which may have a cholesterol lowering effect which blocks the cholesterol absorption and excrete it in stool [14].

There is a reported effect of anti hyperlipidimic activity of *L.siceraria*on total cholesterol, triglycerides and LDL with increased in HDL levels in rats [4]. Moreover, Lipid lowering effect is due to the presence of sterols in LSFJ campesterol, fucosterol, and fixed oil, which is considered as good source of mono- and polyunsaturated fatty acids and cardiac aglycones[15]. Serum levels of plant sterols are regulated by their dietary intake, intestinal absorption, and biliary secretion. They have been reported to correlate negatively with cholesterol synthesis and positively with cholesterol absorption [16]. Castro-Gago and Novo-Rodriguez performed a prospective study which showed increased level of serum lipids due to antiepileptic drug are transient, reversible and influenced by low fat diet[17].

CONCLUSION

Carbamezapine showed high lipidimic activity in both male and females rabbits especially in LDL ratio which may be one of the risk factor for atherosclerosis. LSFJ reduced LDL and total cholesterol in both gender therefore, reduced the risk of atherosclerosis and related disease. Plant proteins are considered as less hyperlipidemic than animal proteins hence very effective in to maintain weight. Therefore, a Co therapy with *Lagenaria*

siceraria (lipid lowering diet) with carbamezapine (drug) proves to be effective in obesity and has a protective effect in high cholesterol against the drugs which cause hyperlipidemia.

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