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ANTIDIABETIC AND ANTIHYPERLIPIDEMIC ACTIVITY OF *CHONEMORPHA FRAGRANS* AND *ERYTHROXYLUM MONOGYNUM* COMBINED ETHANOLIC LEAF EXTRACT IN ALLOXAN INDUCED DIABETIC WISTAR RATS

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ABSTRACT

The objective of the present study was to evaluate the antidiabetic and antihyperlipidemic activity of herbal formulation containing *Chonemorpha fragrans* and *Erythroxylum monogynum* in alloxan induced diabetic rats. Diabetes mellitus is a group of syndrome characterized by hyperglycemia, altered metabolism of lipids, carbohydrates and proteins and an increased risk of complications from vascular diseases. Hyperlipidemia constitutes a major etiopathological factor for atherosclerosis. The preliminary phytochemical screening shows the presence of alkaloids, glycosides, carbohydrates, flavonoids, tannins, saponins, sterols, phenols and proteins. The antidiabetic and antihyperlipidemic effect of combined herbal formulation was studied in alloxan (150mg/kg b.w., i.p.) induced diabetes in wistar rats for doses 200 mg/kg b.w. and 400 mg/kg b.w. (p.o.) daily for 21 days, and the effect was compared with oral dose of 5mg/kg, b.w. glibenclamide. The effect of ethanolic leaf extracts of *Chonemorpha fragrans* and *Erythroxylum monogynum* on blood glucose, serum lipid profile total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), very low density lipoprotein cholesterol (VLDL-C) were measured in the diabetic rats. Diabetes caused by alloxan treatment increases the level of glucose and biochemical parameters in blood sample but treatment with combined herbal formulation, protects from diabetes and significantly decreases the elevated blood glucose, LDL, VLDL levels, total cholesterol levels and total triglycerides levels & increases the HDL levels. In conclusion the present study indicates that the combined ethanolic leaf extracts of plants *Chonemorpha fragrans* and *Erythroxylum monogynum* possesses significant antidiabetic, antihyperlipidemic activity in alloxan induced diabetic rats.

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ITRODUCTION

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia, abnormal lipid and protein metabolism along with specific long-term complications affecting the retina, kidney and nervous system [1]. Hyperglycemia is an important factor in the development and progression of the complications of diabetes mellitus [2]. The pathogenesis of diabetes mellitus is managed by insulin and oral administration of hypoglycemic drugs such as sulfonylureas and biguanides [3]. Unfortunately, apart from having a number of side effects, none of the oral synthetic hypoglycemic agents has been successful in maintaining euglycaemia and controlling longterm microvascular and macrovascular complications [3-5]. The toxicity of oral antidiabetic agents differs widely in clinical manifestations, severity and treatment [6]. The use of herbal medicines for the treatment of diabetes mellitus has gained importance throughout the world. The World Health Organization also recommended and encouraged this practice especially in countries where access to the conventional treatment of diabetes is not adequate [7]. There is an increased demand to use natural products with antidiabetic activity due to the side effects associated with the use of insulin and oral hypoglycemic agents [8, 9]. The available literature showed that there are more than 400 plant species having hypoglycemic activity [10-12]. Though some of these plants have great reputation in the indigenous system of medicine for their antidiabetic activities, many remain to be scientifically established. Hypercholesterolemia and hypertriglyceridemia are common complications of diabetes mellitus in addition to hyperglycemia [13-15]. The frequency of hyperlipidemia in diabetes is indeed very high, depending on the type of diabetes and its degree of control [16].Despite the introduction of hypoglycemic agents from natural and synthetic sources, diabetes and its secondary complications continue to be a major medical problem. Many indigenous Indian medicinal plants have been found to be useful to successfully manage diabetes. One of the great advantages of medicinal plants is that these are readily available and have no side effects [17]. World Health Organization (WHO) [18] has suggested the evaluation of the potential of plants as effective therapeutic agents, especially in area which we lack safe modern drugs.

Medicinal plants play important roles in the management of type II diabetes especially in resource limited countries. In India, herbal medicines including polyherbal therapy is widely practiced. The combination of various types of agents from different plant sources could have synergistic, potentiative, antagonistic pharmacological and therapeutic effects with minimum side effects [19].*Chonemorpha fragrans* belongs to family Apocynaceae. It is a medicinal herb used in the indigenous system of medicine. Roots are useful in vitiated conditions of vata and kapha, skin diseases, leprosy, scabies. Roots of this plant are useful in dyspepsia, colic, constipation hyperacidity, cardiac debility, diabetes, jaundice, cough, bronchitis and intermittent fevers. It is also used in the treatment of diarrhea, polyuria, boils, leprosy, eye diseases, vomiting and poisoning [20].The leaf juice intake purifies blood. The leaf paste is applied on the affected part to cure skin diseases [21].Plant possess skeletal muscle relaxant effect & also used as antispasmodic. Roots & leaves are mostly effective in stomach problems. Leaves are used in the form of churna or extract and in combination with the other plant materials in their formulation administered orally. VS Shende et al found that the alcoholic extract of roots of *Chonemorpha fragrans* significantly reduced the blood glucose levels [22].

Erythroxylum monogynum belonging to family Erythroxylaceace is a medicinal herb. Leaves raw or cooked are eaten to a considerable extent in times of famine. They contain a bitter tonic principle which might serve to relieve the pangs of hunger. Biological activity of the plant is hypothermic & CNS active. Leaf is diaphoretic, stimulant, diuretic, stomachic. A decoction is used for malarial fever.Leaf juice given orally as a cooling beverage and also administered for treating jaundice. Leaves crushed with black pepper and the extract is given orally to kill the intestinal worms. Stem bark decoction is used to treat hiccups and given orally in morning time on empty stomach for 4 weeks to treat itches .Bark and wood are used as febrifuge. Infusion of the wood and bark is considered as stomachic, diaphoretic and diuretic. Oil from the seed is used to cure psoriasis, skin diseases. General stimulant other effects are related to the potentiation of responses of sympathetically innervated organs to catecholamines, and to sympathetic nerve stimulation causing tachycardia and mydriasis. It is used as ophthalmic anaesthetic. Fruits are consumed to cure indigestion. Paste of roots in warm water is used to cure cough and skin diseases. Methanolic extract of leaves showed hepatoprotective activity [23]. Methanolic extracts of aerial parts of *E.monogynum* showed cytotoxic action against brine shrimps & antitumour activity against the tumors induced by *Agrobacterium tumefaciens* using carrot disc anti-tumour bioassay [24]. *E.monogynum* also possesses antioxidant activity [25]. Phytochemical analysis & screening of antibacterial activity of the methanol and acetone leaf extracts of *C.guianensis* and *E.monogynum was* carried out against Escherchia coli, Klebsiela pneumoniae, Pseudomonas putida and Staphylococcus aureus & it was found to possess antibacterial activity [26].

The objective of this research was to investigate the antidiabetic and antihyperlipidemic activity of ethanolic combined leaf extracts of *Chonemorpha fragrans* and *Erythroxylum monogynum* by estimation of blood glucose levels and plasma lipid profile such as total cholesterol, triglyceride, high density lipoprotein, very low density lipoprotein and low density lipoprotein in alloxan induced diabetic rats.

MATERIALS & METHODS

Plant material

The leaves of *Chonemorpha fragrans* (Moon) Alston family Apocynaceae and *Erythroxylum monogynum* (Roxb) Hochr family Erythroxylaceae were collected from botanical gardens of Sri Venkateshwara University Tirupati. The species were taxonomically identified and authenticated by Dr. Madhava Chetty, Assistant professor of Botany, Department of Pharmacognosy, Sri Venkateshwara University, Tirupathi.

Chemicals

Alloxan monohydrate was obtained from Universal Chemical Corporation Abids, Hyderabad. Glibenclamide was obtained as gift sample from Aurobindo pharma. All the chemicals and reagents used for the present study were of analytical grade.

Preparation of extract:

The leaves of *C.fragrans* (C.F) and *E.monogynum* (E.M) were shade dried in room temperature for about 10days and then powdered which were later extracted by cold maceration technique using ethanol as solvent for 7 days with intermittent shaking. The extracts were evaporated to dryness to get the extract.The extract thus obtained was subjected for evaluation of antidiabetic and antihyperlipidemic activity. The individual extracts of *C.fragrans* (C.F) and *E.monogynum* (E.M) prepared were mixed in equal proportions in normal saline for pharmacological experiments.

Phytochemical evaluation:

Preliminary phytochemical screening was performed as per the standard methods [27].The ethanolic leaf extracts of *C.fragrans* and *E.monogynum* were screened for the presence of various phytochemicals by employing standard conventional protocols [28-30].

Animals:

Healthy adult male wistar rats weighing 180-250gms each were used for the study. Animals were maintained under standard environmental conditions (22-28°C, 60-70% relative humidity, 12hr Light and Dark cycle) and fed with standard feed and water *ad libitum.* The experimental protocol was approved by the Institutional Animal Ethics Committee. All studies were performed in accordance with the guidelines for the care and use of laboratory animals, as adopted and promulgated by the Animal Care committee, CPCSEA (Committee for the purpose of control and supervision of experiments on animals) with clearance no: 001/CEAD/SES/SWCP/14.

Acute toxicity studies:

Acute toxicity study was performed as per Organization for Economic Co-operation and development OECD-425 guidelines. It was observed that there was no gross evidence of any abnormalities up to 4hrs and no mortality was observed in animals up to the end of 48hrs at the maximum tested dose level of 2000mg/kg b.w. in rats. This was considered as Maximum Tolerated Dose (MTD) and thus, 1/10th of MTD i.e., 200mg/kg b.w. was taken as test dose and double the test dose i.e., 400mg/kg b.w. was also selected for the experimental studies.

Induction of diabetes in rats:

Male Wistar rats (180-250gm) were made diabetic by a single i.p injection of Alloxan monohydrate at a dose of 150mg/kg using normal saline as vehicle which was freshly prepared immediately before injection. Alloxan also causes changes in serum lipid profile. The rats were maintained on 5% glucose solution for next 24hrs to prevent hypoglycemia. The diabetic state was confirmed by the measurement of fasting blood glucose concentration

3 days after the alloxan treatment using the blood samples drawn from tail vein .The rats with effective and permanent elevated blood glucose levels above 250mg/dl were considered to be diabetic and were used for the study.

Experimental design:

The diabetic and hyperlipidemic rats were divided into 5 groups, each containing 6animals.

Group I- Normal control rats received normal saline p.o.

Group II - Diabetic control rats received alloxan (150mg/kg) b.w i.p in normal saline p.o.

Group III- Alloxan induced diabetic rats treated with combined ethanolic leaf extract of *Chonemorpha fragrans* (C.F) and *Erythroxylum monogynum* (E.M) at a dose of 200mg/kg b.w, p.o.

Group IV-Alloxan induced diabetic rats treated with combined ethanolic leaf extract formulation of *Chonemorpha fragrans* (C.F) and *Erythroxylum monogynum* (E.M) at a dose of 400mg/kg b.w, p.o.

Group V - Alloxan induced diabetic rats treated with glibenclamide at a dose of 5mg/kg b.w, p.o.

The administrations of extracts were continued for 21days, once daily. Blood samples were collected through the tail vein on days 1, 7, 14 and 21 days after drug administration and the blood glucose levels were estimated using Accu-check glucometer.

Estimation of blood cholesterol:

Serum lipid profile estimation at the end of 21 days, blood was collected from inferior vena cava, serum separated for determination of parameters like total cholesterol, HDL- cholesterol and triglycerides. VLDL cholesterol and LDL-cholesterol were calculated using the Friedewald's formula. VLDL = Triglycerides/5 LDL =Total cholesterol-(HDL-CH+VLDL-CH)

Statistical analysis:

Results were expressed as Mean ± SEM. Statistical analysis were performed with instat software using one way analysis of variance (ANOVA) followed by Dunnet's t -test. P values less than *p<0.05, p**<0.01, p***<0.001 were considered to be statistically significant, when compared with control and standard group as applicable.

RESULTS AND DISCUSSION

Table 1: Phytochemical analysis of ethanolic leaf extracts of *Chonemorpha fragrans* and *Erythroxylum monogynum*.

Type of constituents	*Chonemorpha fragrans* ethanolic leaf extract	*Erythroxylum monogynum* ethanolic leaf extract
Alkaloids	+	+
Glycosides	+	+
Carbohydrates	+	+
Flavonoids	+	+
Tannins	_	+
Saponins	+	+
Sterols	+	+
Phenols	_	+
Proteins	+	_
Triterpenoids	_	_
Anthraquinones	_	_

+ indicates presence and - indicates absence.

Antidiabetic activity:

The effect of *Chonemopha fragrans* (CF) and *Erythroxylum monogynum* (EM) on serum glucose levels in diabetic rats depicted in (Table 2). In animals treated with alloxan (150 mg/kg i.p) (Group II), a significant increase in serum glucose level was observed on 7th, 14th & 21st days when compared with normal rats (Group I). After the oral administration of ethanolic leaf extracts of *Chonemorpha fragrans* and *Erythroxylum monogynum* in diabetic control rats, a significant reduction in blood glucose level was observed on the 7th, 14th and 21st compared with diabetic control rats. Group V received glibenclamide (5mg/kg p.o.) showed decrease in serum glucose level when compared with diabetic control rats (Group II).

Table 2: Effect of ethanolic leaf extracts of *Chonemorpha fragrans* and *Erythroxylum monogynum* on blood glucose levels (mg/dl) in alloxan induced diabetic rats on 1st, 7th, 14th and 21st day of the treatment.

Treatment Groups	1st day	7th day	14th day	21st day
Normal control	97 ±0.83	97.8±1.31	96.5±1.62	96.3±1.65
Diabetic control	257.7±2.37	266.±4.52	271.4±3.12	295.6±2.72
CF & EM treated (200 mg/kg)	249.4±2.06	220.5±3.42	195.2±2.52*	172.4±3.25**
CF & EM treated (400 mg/kg)	245.6±2.45	216.3±2.21*	170.4±3.34**	155.2±2.24**
Glibenclamide treated (5mg/kg)	247.2±3.21	224.1±1.36**	159.4±1.65**	147.3±1.16**

Values are expressed as Mean±SEM (n=6); *P<0.05, **P<0.01, ***P<0.001 was considered significant with respect to control group using ANOVA followed by Dunnett's t-test.

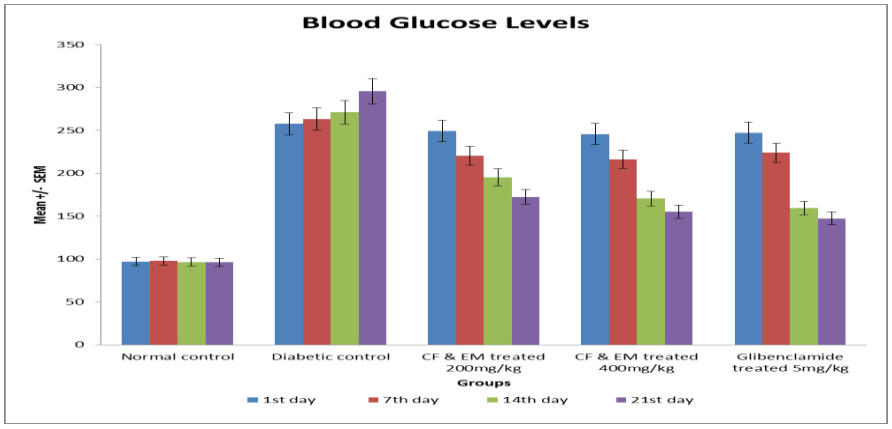


Figure 1: Blood glucose levels (mg/dl) on 1st, 7th, 14th & 21st day of treatment.

Values are expressed as Mean±SEM (n=6); *P<0.05, **P<0.01, ***P<0.001 was considered significant with respect to control group using ANOVA followed by Dunnett's t-test.

Hence the administration of CF and EM combined formulation extract for 21 days decreased the elevated blood glucose levels. The above result suggests that CF and EM combined formulation at a dose of 400mg/kg.b.w was more effective than 200 mg/kg.b.w and was almost comparable with the effect produced by standard drug glibenclamide treated group. The results were represented by means of graph 1 by using ANOVA followed by Dunnett's t-test.

Anti-hyperlipidemic activity:

The lipid profiles in control and experimental rats are depicted in (Table 3) in alloxan induced diabetic rats. The diabetic control rats (Group II) showed significant increase in serum triglycerides, total cholesterol, very low density lipoproteins (VLDL) and low density lipoproteins (LDL) while decrease in High density lipoproteins (HDL) when compared with normal (Group I). The ethanolic extracts of *Chonemorpha fragrans* (CF) *& Erythroxylum monogynum* (EM) showed significant decrease in total cholesterol, LDL, VLDL, triglycerides and significant increase in HDL when compared with diabetic control group (Group II). All these effects were observed on day 21. Standard glibenclamide (Group V) also reduced triglycerides, total cholesterol, very low density lipoproteins (VLDL), low density lipoproteins (LDL) & increased High density lipoproteins (HDL) when compared with diabetic control rats (Group II).The present experimental result indicated that ethanolic extracts exhibited a potent serum lipid lowering properties in alloxan diabetic rats.

Table 3: Effect of ethanolic leaf extracts of *Chonemorpha fragrans* and *Erythroxylum monogynum* on serum lipid profile in alloxan (150mg/kg b.w) induced diabetic rats after 21 days of treatment:

Groups	Serum Low Density Lipoprotein(LDL) (mg/dl)	Serum Very Low Density Lipoprotein(VLDL) (mg/dl)	Serum High Density Lipoproteins (HDL)(mg/dl)
Normal control	40.56±2.61***	18.64±0.92***	38.82±0.50***
Diabetic control	92.57 ± 2.19	37.42± 4.12	24.63± 3.24
CF &EM treated (200 mg/kg)	45.64±0.56***	24.35±0.42**	34.87±0.25**
CF & EM treated (400mg/kg)	36.21±0.38***	21.74±0.47***	39.45 ±0.46***
Glibenclamide treated (5mg/kg)	35.16±0.25***	20.43±0.58***	40.62 ±0.33***

Values are expressed as Mean±SEM (n=6); *P<0.05, **P<0.01, ***P<0.001 was considered significant with respect to control group using ANOVA followed by Dunnett's t-test.

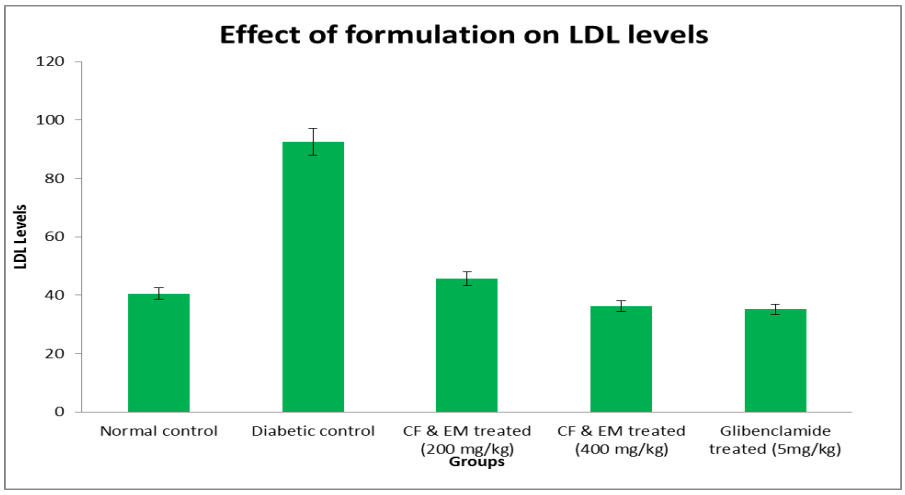


Figure 2: Effect of ethanolic extracts of the leaves of medicinal plants on serum low density lipoprotein (ldl)(mg/dl).

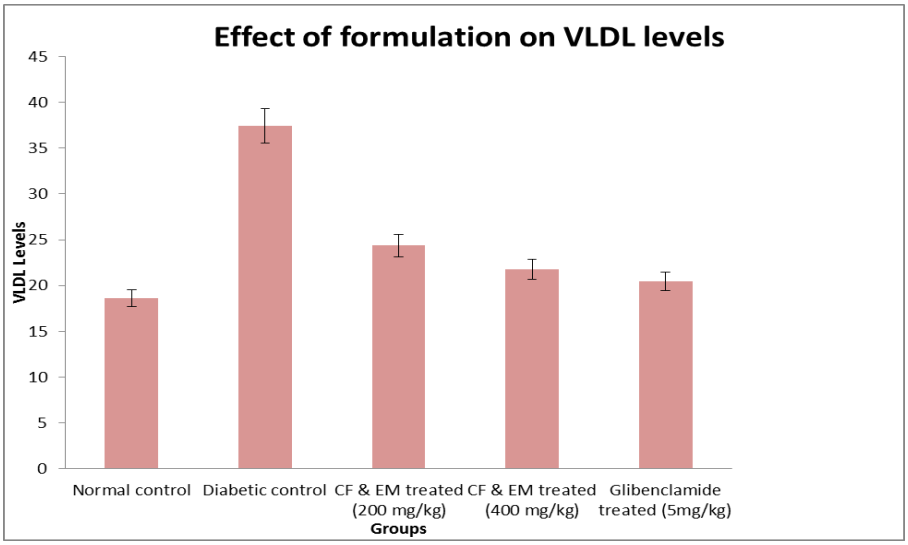


Figure 3: Effect of ethanolic extracts of the leaves of medicinal plants on serum very low density lipoprotein (Vldl)(mg/dl).

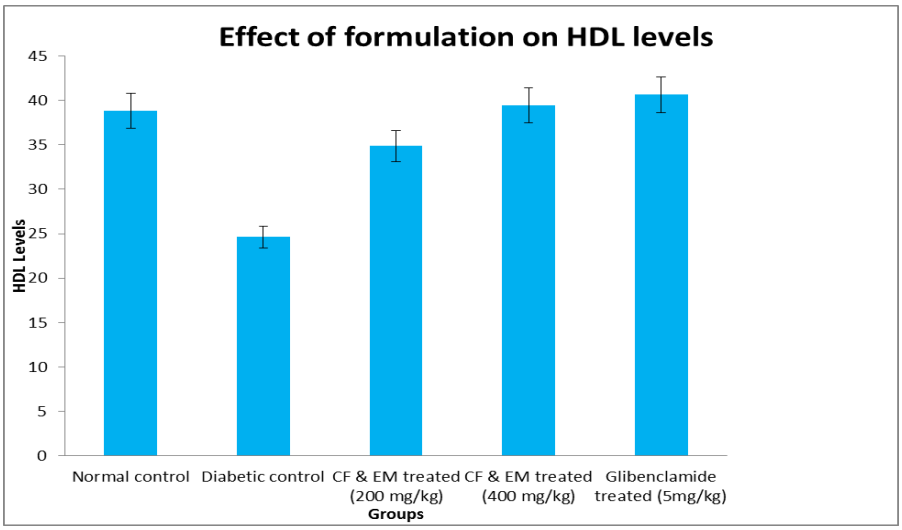


Figure 4: Effect of ethanolic extracts of the leaves of medicinal plants on serum high density lipoprotein (hdl)(mg/dl).

Table 4: Effect of ethanolic leaf extracts of *Chonemorpha fragrans* & *Erythroxylum monogynum* on serum total cholesterol, triglycerides & cholesterol ratio in alloxan (150mg/kg b.w) induced diabetic rats after 21 days of treatment:

Groups	Total cholesterol (mg/dl)	Total triglycerides (mg/dl)	Cholesterol ratio = tc/hdl
Normal control	88.48±0.18***	82.72±0.45***	2.27±0.025
Diabetic control	148.33± 5.89	164.47 ± 1.40	6.02±0.47
CF & EM treated (200 mg/kg)	106.42±0.44**	115.35±0.56*	3.05±0.085**
CF & EM treated (400 mg/kg)	91.73±0.48***	95.46± 0.69**	2.32±0.0602**
Glibenclamide treated (5 mg/kg)	90.24±0.48***	96.14±0.84***	2.22±0.105**

Values are expressed as Mean±SEM (n=6); *P<0.05, **P<0.01, ***P<0.001 was considered significant with respect to control group using ANOVA followed by Dunnett's t-test.

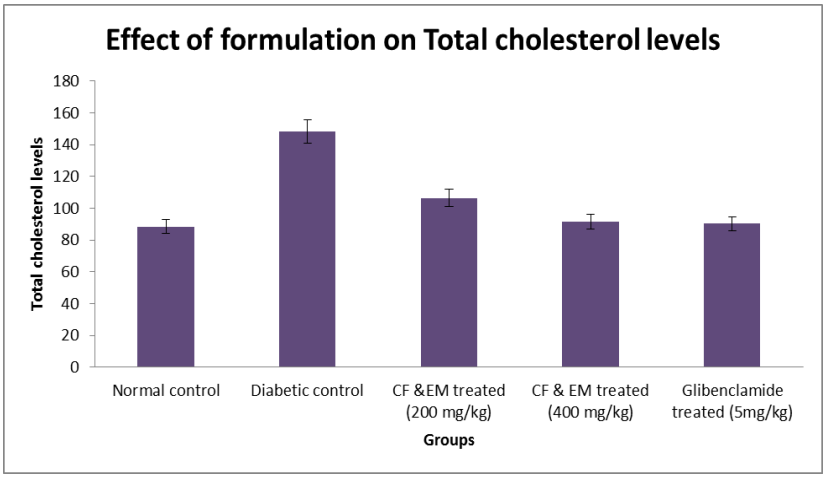


Figure 5: Effect of ethanolic extracts of the leaves of medicinal plants on total cholesterol (mg/dl).

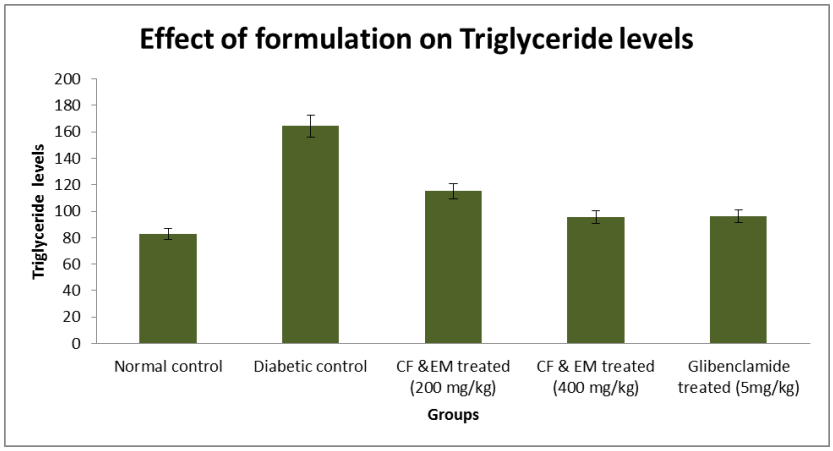


Figure 6: Effect of ethanolic extracts of the leaves of medicinal plants on serum total triglycerides (mg/dl).

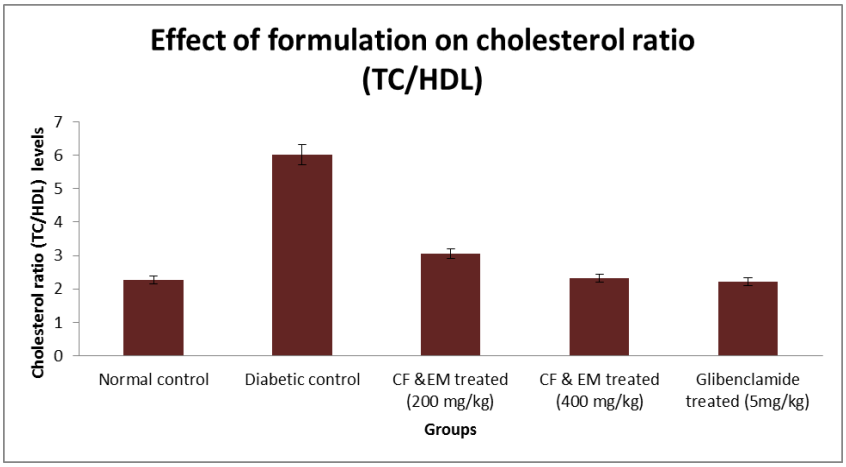


Figure 7: Effect of ethanolic extracts of the leaves of medicinal plants on cholesterol ratio (TC/HDL).

Diabetes Mellitus is a chronic disorder caused by partial or complete insulin deficiency, which produces inadequate glucose control and leads to acute or chronic complications. Premature and extensive atherosclerosis involving renal, peripheral and cardiovascular vessels remain the major complication of diabetes mellitus. Alteration in the serum lipid profile is known to occur in diabetes and is likely to increase the risk of coronary heart disease. A reduction in serum lipids, particularly of LDL, VLDL fraction and triglycerides should be considered as been beneficial for long time prognosis. Lowering of blood glucose level and serum lipid level through dietary medication and drug therapy seems to be associated with the decreased risk of vascular diseases.

Abdominal obesity contributes to insulin resistance, a metabolic abnormality linked to the development of type 2 diabetes mellitus and cardiovascular disease (CVD). Insulin resistance generally precedes the development of type 2 diabetes. The pathophysiologic mechanisms known to increase CVD risk in individuals with insulin resistance include formation of advanced glycation end products (AGE's), hypertension, proinflammatory, prothrombotic states and dyslipidemia (i.e., low levels of high-density lipoprotein cholesterol, increased levels of triglycerides, small, dense low-density lipoprotein cholesterol particles, apoplipoprotein B, and inflammation). Insulin resistance and impaired glucose tolerance are associated with increased CVD risk. Individuals with coexisting metabolic syndrome and diabetes have the highest prevalence rates of CVD. Alloxan induces chemical diabetes in a wide variety of animal species by damaging the insulin secreting pancreatic β-cells resulting in the decreased endogenous insulin release. Reduced insulin secretion and defective insulin function results in enhanced metabolism of lipids from adipose tissue to the plasma. Impairment in insulin sensitivity due to high concentration of lipids in the cells is responsible for cardiovascular risk in diabetes mellitus. Thus altered lipid and lipoprotein pattern observed in diabetic rats could be due to defect in insulin secretion and action. Hypercholesterolemia and hypertriglyceridemia have been reported to occur in diabetic rats. Accumulation of cholesterol and phospholipids in liver is due to elevated plasma free fatty acids.

In the present study, the combined ethanolic leaf extracts of *Chonemorpha fragrans* & Erythroxylum *monogynum* significantly decreased the blood glucose level in alloxan induced diabetic rats as compared with standard group which clearly indicates that it possess a glucose lowering effect and lipid lowering effect. It was also found to be highly effective in managing complications associated with diabetes mellitus such as atherosclerosis, hyperlipidemia etc.

CONCLUSION

From the present experimental findings, it is concluded that the ethanolic extracts of leaves of *Chonemorpha fragrans* and *Erythroxylum monogynum* exhibited promising antidiabetic and antihyperlipidemic activity in alloxan induced diabetic rats. Hence, *Chonemorpha fragrans* and *Erythroxylum monogynum* can be helpful in the management of diabetes mellitus, hyperlipidemia and other associated complications.

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