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EVALUATION OF ANTIDIABETIC AND ANTIHYPERLIPIDEMIC ACTIVITY OF METHANOLIC ROOT EXTRACTS OF *WITHANIA SOMNIFERA*, *BOERHAAVIA DIFFUSA* AND THEIR COMBINATION IN DEXAMETHASONE INDUCED DIABETIC RATS

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Keywords:

Diabetes mellitus, *Withania somnifera*, *Boerhaavia diffusa*, Dexamethasone, MEWS: Methanolic Extract of *Withania somnifera*, MEBD: Methanolic Extract of *Boerhaavia diffusa*, HDL: High density lipoproteins, LDL: Low-density lipoproteins, VLDL: Very low-density lipoproteins

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ABSTRACT: Diabetes mellitus is one of the major public health problems throughout the world. Current therapies, especially synthetic drugs, often fail to bring back normal glycemic control without complications. Numerous herbal medicines are widely explored as alternative medicine in diabetes. The objective of this work was to evaluate the antidiabetic activity of such herbal extracts of roots of *Withania somnifera*, *Boerhaavia diffusa*, and their combination in experimentally induced diabetic rats. Both plants are well known for their potential medicinal activities. The two plant extracts and their combination at a dose of 200 mg/kg/day were administered to dexamethasone-induced insulin-resistant animals for 10 consecutive days. Blood glucose levels, lipid profiles, and body weights were measured for the evaluation of their anti-diabetic effect. MEWS ($p<0.05$), MEBD ($p<0.01$), and their combination ($p<0.001$) showed a significant decrease in blood glucose levels in diabetic rats. In addition, both the extracts ($p<0.05$), ($p<0.01$), ($p<0.05$) ($p<0.05$) and their combination ($p<0.01$), ($p<0.001$), ($p<0.001$), ($p<0.01$) showed significant decrease in serum triglycerides, total cholesterol, VLDL levels, and an increase in HDL levels respectively. The combination ($p<0.01$) showed a significant decrease in LDL levels, whereas the individual extracts have no significant difference. The combination of MEWS and MEBD showed a significant ($p<0.01$) increase in body weight in diabetic rats. Our study indicates that MEWS, MEBD, and their combination have a promising effect in controlling blood glucose levels and also aid in counteracting the derangement of lipid profile, a major concern in diabetes mellitus.

INTRODUCTION: Diabetes mellitus is a major health problem globally. It is a metabolic disorder characterized by hyperglycemia [1]. In this condition, the major metabolic pathways of carbohydrates, lipids and proteins will be altered [2].

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Apart from these, it also leads to severe complications like diabetic ketoacidosis, diabetic neuropathy, Microangiopathy, *etc.* [3] Although there are several novel medicines available today, their use is often limited. So the search for herbal medicine continues, as they show minimal or no severe complications.

It is clearly known that diabetes mellitus is classified into two main types of *viz.* Insulin Dependent Diabetes Mellitus (IDDM) and Non-Insulin Dependent Diabetes Mellitus (NIDDM). In recent times, steroid-induced diabetes is of major

concern [4]. Steroid-induced diabetes mellitus is defined as an abnormal increase in blood glucose associated with the use of glucocorticoids in a patient with or without a prior history of diabetes mellitus [5].

The major symptom of steroid-induced diabetes is hyperglycemia and alteration in the lipid profile. The effect of glucocorticoids on glucose metabolism is likely the result of impairment of multiple pathways, which includes insulin resistance, pancreatic β- cell dysfunction, glycero-neogenesis.

Withania somnifera (L.) Dunal is of high medicinal value, itis cosmopolitan, and grows throughout the drier parts and subtropical regions. It is commonly known as Ashwagandha, and it contains the chemical constituents like alkaloids, salts, steroids, flavonoids, *etc.* [6] The different plant parts of ashwagandha possess abortifacient, adaptogenic, alterative, analgesic, antiarthritic, antiasthmatic, antibiotic, antidyspeptic, anti-inflammatory, anti-mitotic, antiproliferative, antitumor, aphrodisiac, astringent, bactericide, carminative, contraceptive, depurative, diuretic, emetic, febrifuge, fungicidal, hypnotic, immune-modulating, laxative, proteolytic, tonic and nervine sedative properties.

Additionally, it may have cytotoxic, chemo-preventative, and radiosensitizing actions [7]. *Boerhaavia diffusa* Linn occupied a reputed position of having valuable medicinal properties in both folk and classical streams of indigenous medicinal systems.

It is pungent, astringent, and bitter in taste; the various parts of the plant are used in the treatment of cancer, jaundice, dyspepsia, and inflammation. It is commonly known as Punarnava, and it contains the chemical constituents like alkaloids, steroids, flavonoids, *etc.* [8]

MATERIALS AND METHODS:

Collection and Authentication of Plant Material: The dried roots of the plants *Withania somnifera* and *Boerhaavia diffusa* were obtained from Vijaya Ayurvedic stores, Kakinada, East Godavari district, Andhra Pradesh, India. The plants were identified and authenticated by Prof. A. Srinivasa Rao, Head of the Botany department, P. R. Government Degree College, Kakinada.

Preparation of Extracts: The dried roots of both the plants were pulverized to a coarse powder. Five hundred gms dried root powder of each of the two plants was extracted with 80% v/v methanol by Maceration. The coarsely powdered plant material was soaked in methanol in a closed container and allowed to stand for about a week with occasional stirring. After the complete extraction, the extract was filtered, and the solvent was distilled off. The extract was concentrated to dry residue. The percentage yield of the extract was calculated with reference to air-dried powder. The percentage yield of Withania and Boerhaavia was found to be 3 and 2.5%, respectively.

Phytochemical Analysis: Phytochemical tests were performed to determine the chemical constituents present in the plant extracts. The extract of Withania showed the presence of carbohydrates, glycosides, alkaloids, steroids, phenols, proteins, and flavonoids; similarly, the extract of Boerhaavia showed the presence of glycosides, alkaloids, steroids, saponins, and flavonoids.

Experimental Animals: Wistar albino rats (150-200 gm) of either sex were used for this study. The animals were procured from Ghosh Enterprises, Kolkata. The animals were acclimatized for one week prior to the study. They were properly housed in polypropylene cages under standard laboratory conditions (12/12 h light/dark cycle at 25 ± 50 ºC) and allowed to free access to a standard dry pellet diet and water *ad libitum*.

After acclimatization, the animals were divided into 6 groups, comprising of 6 rats of either sex in each group. Animals were fasted overnight with free access to water prior to the study. The experimental protocol was approved by the Institutional Animal Ethical Committee (Approval no: 12/2016/CPCSEA)

Induction of Insulin Resistance: The insulin resistance in the experimental animals is induced by the subcutaneous injection of Dexamethasone at a dose of 5 mg/kg body weight for ten days.

Preparation of Dosing: The dose 200 mg/kg body weight of *Withania somnifera* and *Boerhaavia diffusa* root extracts was selected with reference to the acute toxicity studies of the plants [9, 10].

The suspensions of the methanolic extracts of both plants were prepared by using 3.5% Tween-80 in normal saline solution.

Grouping of Animals: The present study was carried out for 11 days to evaluate the effect of *W. somnifera*, *B. diffusa* extracts and their combination on various biochemical parameters like Blood glucose, Triglycerides, Total Cholesterol, HDL, LDL and VLDL in Dexamethasone induced insulin resistance in albino rats. The animals were randomly divided into six groups, with six animals of either sex in each group. The animals were divided into six groups, as follows:

Group I:
Normal Control: The animals in this group are non-diabetic, and they were administered normal saline 2 ml/kg (vehicle) (p.o) for 10 days.

Group II:
Diabetic Control: The animals in this group were administered Dexamethasone 5 mg/kg (s.c) + vehicle (p.o) for 10 days.

Group III:
Standard: The animals in this group were administered Dexamethasone 5 mg/kg (s.c) + Metformin 5 mg/kg (p.o) for 10 days.

Group IV:
Extract 1: The animals in this group were administered Dexamethasone 5 mg/kg (s.c) + Methanolic root extract of *Withania somnifera* 200 mg/kg (p.o) for 10 days.

Group V:
Extract 2: The animals in this group were administered Dexamethasone 5 mg/kg (s.c) + Methanolic root extract of *Boerhaavia diffusa* 200 mg/kg (p.o) for 10 days.

Group VI:
Combination: The animals in this group were administered Dexamethasone 5 mg/kg (s.c) + combined plant extract 200 mg/kg (p.o) *i.e. W. somnifera* 100 mg/kg and *B. diffusa* 100 mg/kg for 10 days. On the last day of the study, *i.e.*, 11^{th} day, the overnight fasted animals were anesthetized with diethyl ether, and the blood was collected by retroorbital puncture method. The blood samples were allowed to clot, and then the serum is separated from the samples by centrifugation at 5000 rpm for 10 min. The samples were stored at refrigeration temperature until use. The biochemical parameters- fasting blood glucose, Triglycerides, Total Cholesterol, HDL, LDL and VLDL were estimated from the collected serum using a semi autoanalyzer. One animal from each of the respective groups is sacrificed by cervical dislocation method. The livers were isolated and Histopathological studies were carried out.

Statistical Analysis: The values obtained for each biochemical parameter and changes in body weight of the animal groups were subjected to column statistical analysis to obtain the mean ± S.E.M for the group. The differences were compared using one-way analysis of variance (ANOVA) followed by Dunnett's test (Graph Pad Prism 5 for Windows, version 5.03, U.S.A), p values <0.05 were considered as significant.

RESULTS:

Biochemical Parameters: Effect of methanolic root extracts of *Withania somnifera* and *Boerhaavia diffusa* and their combination on blood glucose levels: Administration of dexamethasone s.c. for 10 days resulted in an increase in fasting blood glucose levels in Group-II (Diabetic control). Group-I (Normal) rats did not exhibit any such changes. The difference between the two groups was highly significant ($p<0.001$).

TABLE 1: DATA SHOWING CHANGES IN THE FASTING BLOOD GLUCOSE LEVELS AFTER-TREATMENT PERIOD

Group	Treatment	Mean ± S.E.M
I	Normal control	81.5±1.76
II	Dexamethasone induced diabetic control	$460±55.77^{+++}$
III	Diabetic group treated with Metformin 5 mg/kg	$228.66±8.95^{***}$
IV	Diabetic group treated with MEWS 200 mg/kg	$350.66±23.84^{*}$
V	Diabetic group treated with MEBD 200 mg/kg	$316±14.61^{**}$
VI	Diabetic group treated with combination of MEWS & MEBD 200 mg/kg	$276.33±11.13^{***}$

All the values are Mean ± S.E.M, n=6, One way ANOVA followed by Dunnett's Test+ When compared with Normal control; * When compared with Diabetic control+++ / ***p<0.001; ++/**p<0.01; +/*p<0.05 MEWS: Methanolic Extract of *Withania somnifera*, MEBD: Methanolic Extract of *Boerhaavia diffusa*

Administration of Metformin (Group-III), MEWS (Group-IV), MEBD (Group-V), Combination of MEWS, and MEBD (Group-VI) orally for 10 days resulted in a corresponding decrease in fasting blood glucose levels. The change in the fasting blood glucose levels in Group-III was highly significant ($p<0.001$); in Group-IV, it was mildly significant ($p<0.05$); in Group-V, it was moderately significant ($p<0.01$) whereas it is highly significant ($p<0.001$) in Group-VI.

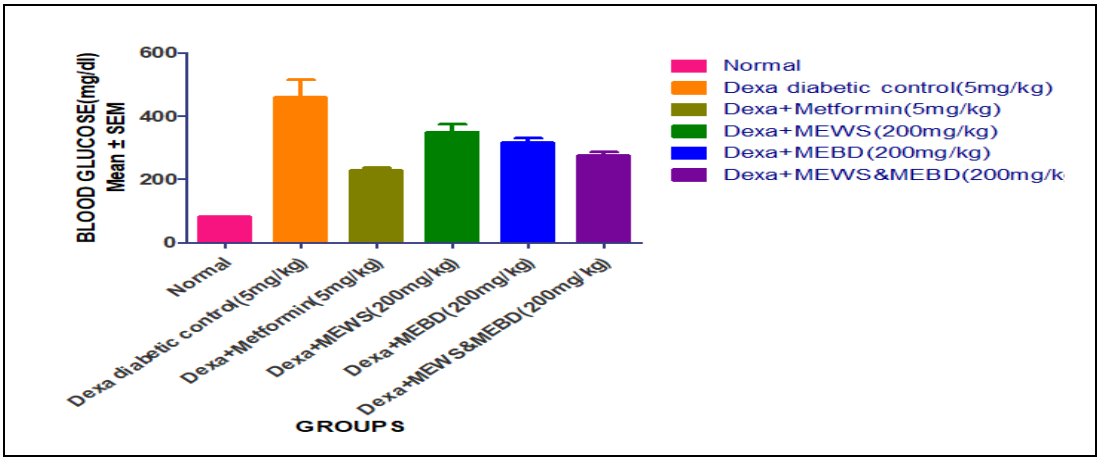

FIG. 1: GRAPHICAL REPRESENTATION OF CHANGES IN THE FASTING BLOOD GLUCOSE LEVELS

Effect of Methanolic Root Extracts of *Withania somnifera* and *Boerhavia diffusa* and their Combination on Lipid Profile: Administration of dexamethasone s.c. for 10 days resulted in an increase in serum triglycerides (TG), total cholesterol (TC), low-density lipoprotein(LDL), very low-density lipoprotein (VLDL) and a decrease in high-density lipoprotein (HDL) levels in Group-II. The normal control did not exhibit any such changes. The difference between the two groups was highly significant ($p<0.001$) for all the above parameters. Administration of Metformin (Group-III), MEWS (Group-IV), MEBD (Group-V), Combination of MEWS and MEBD (Group-VI) orally for 10 days resulted in a corresponding decrease in TG, TC, LDL, VLDL and an increase in HDL levels. The decrease in the TG levels in Groups- III and VI was moderately significant ($p<0.01$) and mildly significant ($p<0.05$) in Groups-IV and V. The decrease in the TC levels in Groups-III and VI were highly significant ($p<0.001$) and moderately significant ($p<0.01$) in Groups-IV & V. The decrease in the VLDL levels in Groups-III & VI was moderately significant ($p<0.01$) and mildly significant ($p<0.05$) in Groups-IV & V. The decrease in the LDL levels in Group-VI was moderately significant ($p<0.01$), mildly significant ($p<0.05$) in Group-III and not significant in Groups-IV & V. The increase in the HDL levels was highly significant ($p<0.001$) in Group-VI, moderately significant ($p<0.01$) in Group-III and mildly significant ($p<0.05$) in Groups-IV & V.

TABLE 2: DATA SHOWING CHANGES IN THE FASTING LIPID PROFILE LEVELS AFTER-TREATMENT PERIOD

Group	Treatment	Mean ± S.E.M				
		TG	TC	HDL	LDL	VLDL
I	Normal Control	85 ± 4.61	86 ± 5.77	31 ± 2.33	100 ± 6.62	17 ± 0.92
II	Diabetic Control	145.16 ± 13.02^{+++}	132.5 ± 2.89^{+++}	21.66 ± 1.28^{++}	125.13 ± 3.70^{+}	29.03 ± 2.60^{+++}
III	Metformin Treated (5 mg/kg)	108.5 ± 5.48**	91.5 ± 6.62***	36.16 ± 1.57**	100.63 ± 7.44*	21.7 ± 1.09**
IV	MEWS Treated (200 mg/kg)	119.66 ± 3.80*	102.33 ± 5.11**	28.5 ± 1.66*	105.4 ± 6.03^{ns}	23.93 ± 0.76*
V	MEBD Treated (200 mg/kg)	119.83 ± 3.43*	101.83 ± 6.19**	28.16 ± 1.81*	105.36 ± 5.81^{ns}	23.96 ± 0.68*
VI	Combination (200 mg/kg)	107.83 ± 4.68**	81.16 ± 4.94***	35.16 ± 1.07***	95.3 ± 5.82**	21.56 ± 0.93**

All the values are mean± S.E.M, n=6, One way ANOVA followed by Dunnett's Test + When compared with Normal control; * When compared with Diabetic control, +++/***p<0.001; ++/**p<0.01; +/*p<0.05; ns not significant MEWS: Methanolic Extract of *Withania somnifera*, MEBD: Methanolic Extract of *Boerhaavia diffusa*

Graphical Representation of Changes in Lipid Profile:

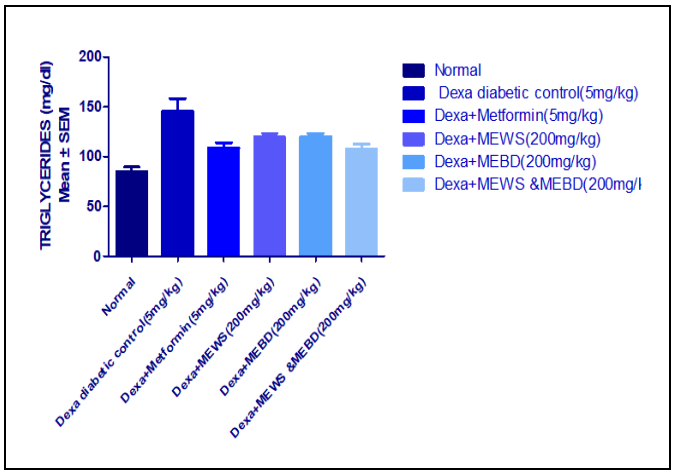

FIG. 2: TRIGLYCERIDES

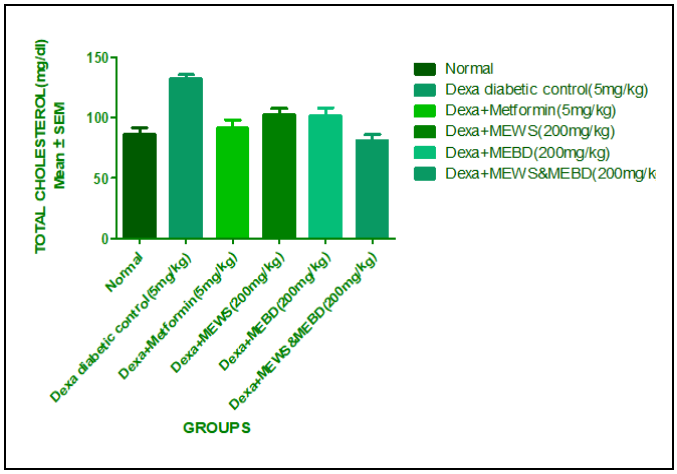

FIG. 3: TOTAL CHOLESTEROL

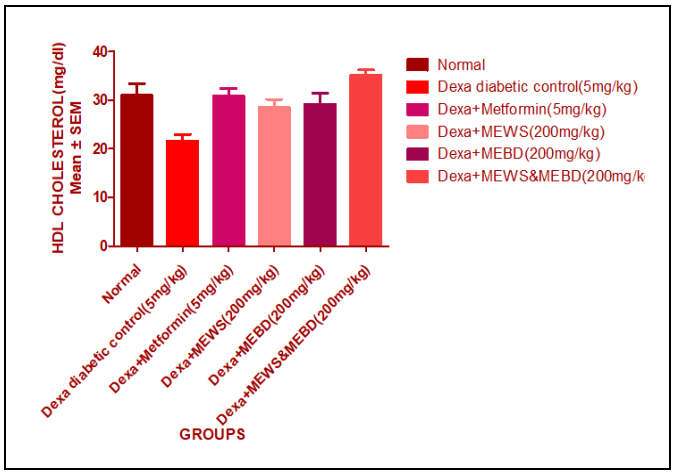

FIG. 4: HDL CHOLESTEROL

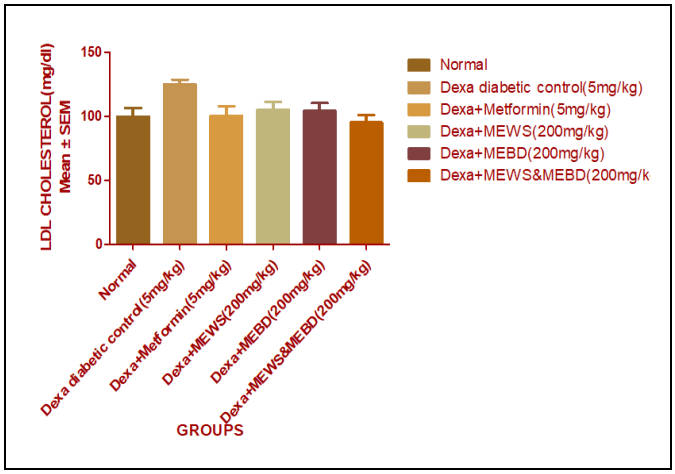

FIG. 5: LDL CHOLESTEROL

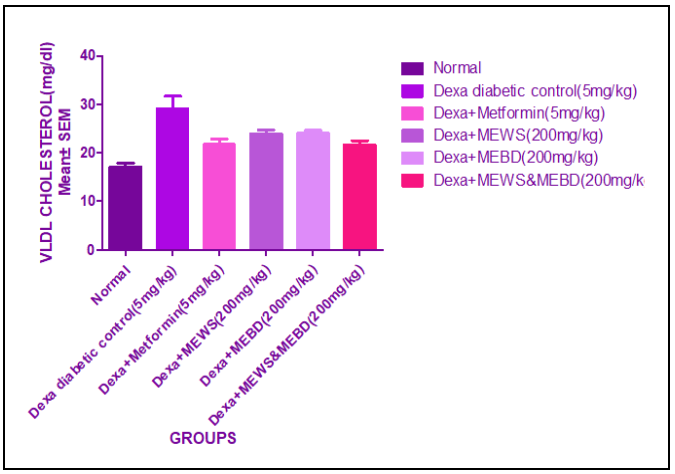

FIG. 6: VLDL CHOLESTEROL

Effect of Methanolic Root Extracts of *Withania somnifera* and *Boerhavia diffusa* and their Combination on Body Weight: MEWS ($p<0.05$) and MEBD ($p<0.01$) and their combination showed significant ($p<0.05$) body weight variation, where dexamethasone ($p<0.001$) decreased body weight when compared with normal rats. MEWS treated group increased body weight than MEBD treated group, combination as like MEWS increases body weight. Metformin did not show any bodyweight increase.

TABLE 3: DATA SHOWING CHANGES IN BODY WEIGHTS AFTER-TREATMENT PERIOD

Group	Treatment	Mean ± S.E.M
I	Normal control	182.83±4.28
II	Dexamethasone induced diabetic control	140.16±5.19***
III	Diabetic group treated with Metformin 5 mg/kg	141.6±3.97***
IV	Diabetic group treated with MEWS 200 mg/kg	164.3±4.34*
V	Diabetic group treated with MEBD 200 mg/kg	162.6±2.26**
VI	Diabetic group treated with combination of MEWS & MEBD 200 mg/kg	166.8 ±4.01*

All the values are mean± S.E.M, n=6, One way ANOVA followed by Dunnett's Test * When compared with Normal control ***p<0.001; **p<0.01, *p<0.05 MEWS: Methanolic Extract of *Withania somnifera*, MEBD: Methanolic Extract of *Boerhaavia diffu*

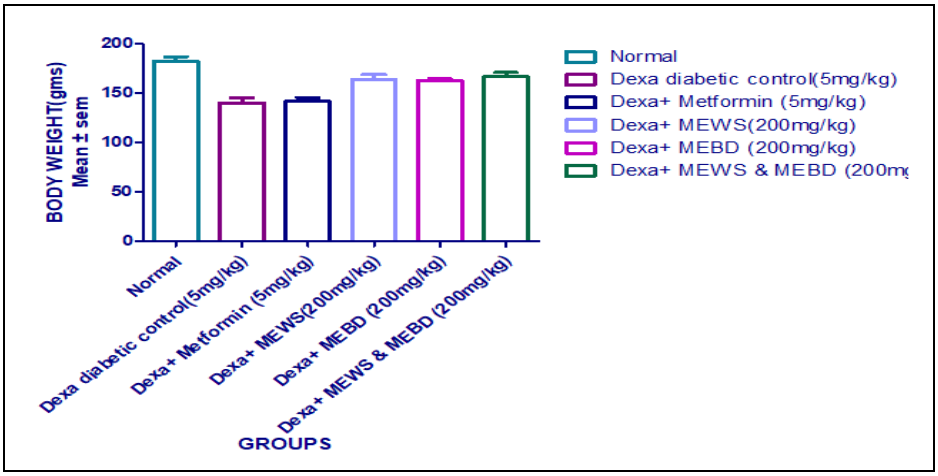

FIG. 7: GRAPHICAL REPRESENTATION OF CHANGES IN BODY WEIGHT

Histopathological Studies:

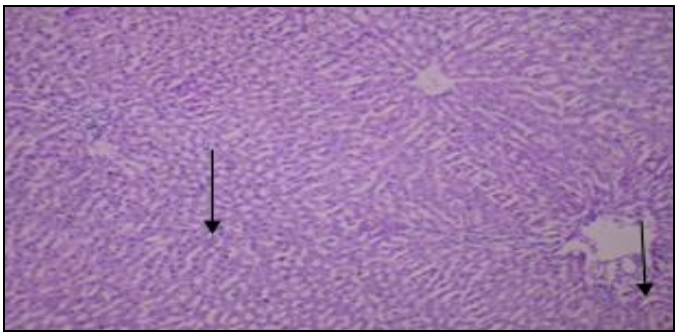

FIG. 8: GROUP-I (NORMAL CONTROL)

Group I: This section show liver parenchyma with intact architecture. The hepatocytes are arranged in array separated by sinusoids. The central vein and portal triad are distinguishable.

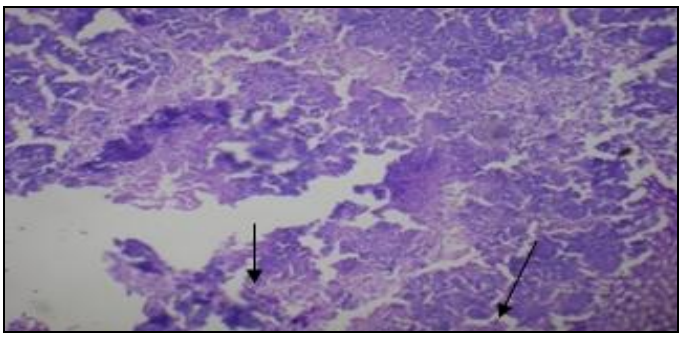

FIG. 9: GROUP-II (DIABETIC CONTROL)

Group II: This section shows entire large areas of necrosis of liver parenchyma with features of karyorrhexis, karyolysis, and pyknosis, and areas of infarction and some hepatocytes show cytoplasmic vacuolations which may be due to glycogen depletion from hepatocytes.

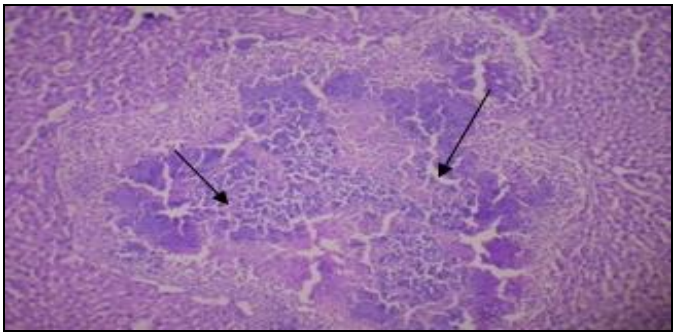

FIG. 10: GROUP-III (METFORMIN TREATED GROUP)

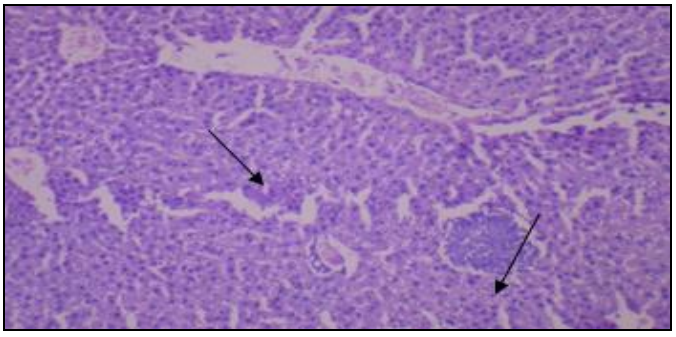

FIG. 11: GROUP-IV (MEWS TREATED GROUP)

Group III: This section shows a large area of necrosis and cytoplasmic vacuolations due to the remarkable depletion of glycogen from the hepatocytes. The architecture of hepatocytes is uneven.

Group IV: This section shows liver structure with occasional areas of liver cells with pink cytoplasm may be due to infarction, and cytoplasmic vacuolations may be due to glycogen depletion.

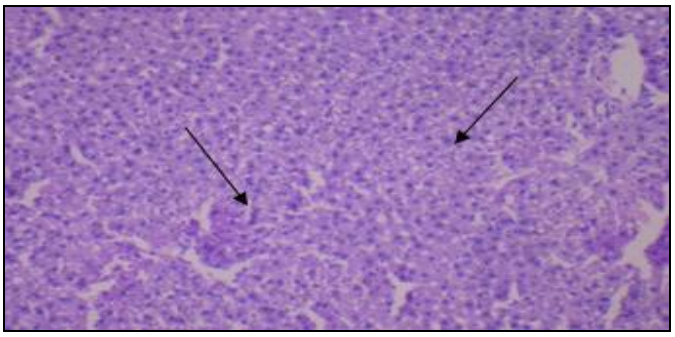

FIG. 12: GROUP-V (MEBD TREATED GROUP)

Group V: This section shows a liver structure with occasional areas of liver cells with pink cytoplasm may be due to infarction, and cytoplasmic vacuolations may be due to glycogen depletion.

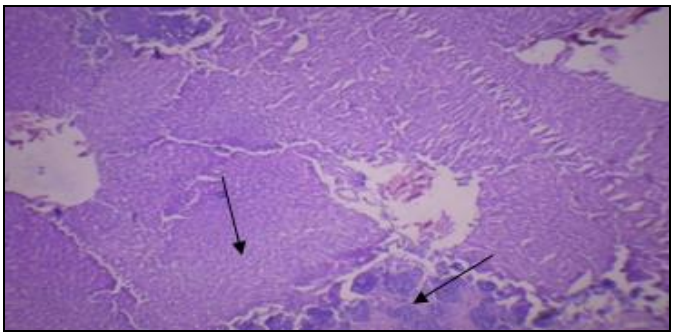

FIG. 13: GROUP-VI (MEWS+MEBD TREATED GROUP)

Group VI: This section shows normal liver structure with dilated central veins and a few areas of necrosis. The cytoplasmic vacuolations are very limited which indicates the restoration of liver glycogen.

DISCUSSION: In view of available literature on *Withania somnifera*, *Boerhaavia diffusa*, an attempt was made to evaluate the antihyperglycemic activity of methanolic root extracts of these molecules and establish a correlation with their positive effect in a reversal of derangement of lipid profile. As mentioned in the results, MEWS ($p<0.05$) and MEBD ($p<0.01$) and their combination showed significant ($p<0.001$) decrease in fasting serum glucose levels when compared with untreated dexamethasone-induced diabetic rats. Similar types of results were observed in the studies of different herbal extracts on dexamethasone-induced diabetes. In this study MEWS ($p<0.05$) and MEBD ($p<0.05$) and their combination showed significant ($p<0.01$) decrease in triglyceride levels, where dexa-methasone ($p<0.001$) increased the triglyceride levels when compared with normal rats.

In this study MEWS ($p<0.01$) and MEBD ($p<0.01$) and their combination showed significant ($p<0.001$) decrease in total cholesterol levels, where dexamethasone ($p<0.001$) increased the total cholesterol levels when compared with normal rats. In this study MEWS ($p<0.05$) and MEBD ($p<0.05$) and their combination showed significant ($p<0.001$) increase in HDL levels, where dexamethasone ($p<0.01$) decreased the HDL levels when compared with normal rats.

In this study MEWS and MEBD showed no significant difference, and their combination showed a significant ($p<0.01$) decrease in LDL levels, where dexamethasone ($p<0.05$) increased the LDL levels when compared with normal rats. In this study MEWS ($p<0.05$) and MEBD ($p<0.05$) and their combination showed significant ($p<0.01$) decrease in VLDL levels, where dexamethasone ($p<0.001$) increased the VLDL levels when compared with normal rats.

Previous studies have shown that the inhibition of Peroxisome proliferated activated receptors (PPAR) could reduce fat and body weight and improve insulin resistance via the modulation of genes related to lipid and glucose metabolism [11, 12, 13]. Many herbal or natural medicines that act as modulators of PPARs, have been reported to block intracellular lipid accumulation and lipogenesis and to improve insulin resistance [14, 15]. In this study MEWS ($p<0.05$) and MEBD ($p<0.01$) and their combination showed significant ($p<0.05$) body weight variation, where dexamethasone ($p<0.001$) decreased body weight when compared with normal rats. MEWS treated group increased body weight than MEBD treated group, combination as like MEWS increases body weight. Metformin did not show any bodyweight increase. The above findings indicate that MEWS and MEBD and their

combination could be used in insulin resistance conditions. Our study suggests that MEWS and MEBD and their combination bringing back glycemic and lipidemic levels to normal in dexamethasone-induced hyperglycemia, hyper-cholesterolemia and hypertriglyceridemia in albino rats. The probable mechanism involved might be improved insulin sensitivity or restored insulin sensitivity in various organs. Further studies into these aspects might reveal the actual mechanisms involved in antidiabetic activity.

CONCLUSION: Our study clearly establishes the hypoglycemic effect of MEWS and MEBD and their combination in dexamethasone-induced diabetic rat models. In addition, there was a good correlation in correcting the lipid de-arrangement commonly seen in diabetic people leading to long-term morbidity and mortality. Since, many anti-diabetic drugs do not correct dyslipidemia, the observed hypolipidemic effect of these plant extracts and their combinations in diabetic rats is quite important. Further investigations are needed to elucidate the exact mechanism of action, particularly the Bioactivity-guided fractionation, isolation-identification, and enzymatic study of constituents of the plant extract responsible for the observed pharmacologic activities.

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CONFLICTS OF INTEREST: Nil

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