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Effect of Isolated Fraction from *Biophytum reinwardtii* on Dexamethasone Induced Insulin Resistance in Rats

Nagaraju Bandaru[1]*, A. Narayana Rao[1], Yasho Deepika[2], Alekhya Ketha[3], Daveedu Thathipudi[4] and N. Sri Laxmi[1]

[1]College of Pharmacy, Koneru Lakshmaiah Education Foundation, Vaddesweram, Guntur - 522502, Andhra Pradesh, India; bnagaraju@kluniversity.in
[2]Department of Pharmacy, Anurag University, Venkatapur, Ghatkesar, Hyderabad - 500088, Telangana, India
[3]Bharat Institute of Technology-Pharmacy, Mangalpally, Hyderabad - 501510, Telangana, India
[4]Department of Biotechnology, Vikarma Simhapuri University, Nellore – 524320, Andhra Pradesh, India

Abstract

The Fraction from Methanolic extract whole plant of *Biophytum reinwardtii* (HEMBR) is traditionally used in the treatment of diabetes. Rats were treated with a standardized dose of Dexamethasone for 14 days and the effect of HEMBR at the doses of 50 and 100 mg/kg, p.o. on plasma blood glucose level, serum triglyceride level, glucose uptake in skeletal muscle, levels of hepatic antioxidant enzymes (GSH, SOD and catalase), and body weight were observed. HEMBR showed a significant decrease in plasma glucose and serum triglyceride levels ($p< 0.01$) at the dose of 50 and 100 mg/kg, p.o. and also stimulated glucose uptake in skeletal muscle. The levels of antioxidant enzymes, GSH, SOD, and catalase were significantly increased ($p< 0.01$). Hence it can be concluded that *Biophytum reinwardtii* may prove to be effective in the treatment of Type-II Diabetes mellitus owing to its ability to decrease insulin resistance.

Keywords: Antioxidants, Diabetes, Fraction, Insulin, Resistance

1. Introduction

Diabetes could be a chronic sickness that happens either once the exocrine gland doesn't manufacture enough hypoglycemic agents, or once the body cannot effectively use the hypoglycemic agent it produces. Insulin could be an internal secretion that regulates glucose[1]. Hyperglycaemia, or raised glucose, could be a typical result of uncontrolled polygenic disease and over time ends up in serious harm to several of the body's systems, especially the nerves and blood vessels[2]. In 2014, 8.5% of adults aged 18 years and older had diabetes. In 2016, diabetes was the direct cause of 1.6 million deaths, and in 2012 high blood glucose was the cause of another 2.2 million deaths[3].

Modern medicines like Biguanides, Sulphonylureas and Thiazolidinediones are available for the treatment of diabetes. But they also have undesired effects associated with their uses[4]. Alternative drugs, notably flavouring medicines are offered for the treatment of polygenic disease. Instead of the introduction of hypoglycemic agents from the synthetic source, diabetes and its secondary complications continue to be a significant problem. Many

**Author for correspondence*

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Indian indigenous medicinal plants are useful to manage diabetes successfully. The main advantages of traditional medicinal plants are that they are readily available and have no side effects. Even the WHO suggested the usage of medicinal plants, especially in areas in lack modern medicines and chronic disorders.

Glucocorticoids are shown to be potent medication and immunological disorder drugs; they began to be used for therapeutic functions within the mid-20th century, and are currently widely used in the treatment of many diseases. Their adverse effects are believed to be caused by a variety of factors, including increased insulin resistance, increased glucose intolerance, reduced β-cell mass from β-cell dysfunction, and increased hepatic insulin resistance leading to impaired suppression of hepatic glucose production[5,6]. The metabolic effects of glucocorticoids on aldohexose metabolism are seen at various stages within the hypoglycemic agent signal cascade. Glucocorticoids reduce peripheral glucose uptake at the level of the muscle and adipose tissue[7,8]. Free fatty acid levels may be elevated in insulin resistance because of impaired insulin-dependent down-regulation of lipolysis, hence leading to elevated levels of triglycerides in muscles as well as other tissues. Triglycerides are reported to be a potent inhibitor of insulin signalling and result in an acquired insulin resistance state[9]. Traditionally *Biophytum reinwardtii* (Oxalidaceae) is used as an antioxidant. Hence the present study was planned to investigate the effect of *Biophytum reinwardtii* on Dexamethasone-induced insulin resistance in rats.

2. Materials and Methods

2.1 Plant Material

Biophytum reinwardtii whole plant was collected from the forest area of Rampachowdavaram, East Godavari and authenticated by Dr P. Prasanna Kumari Department of Botany, D.N.R College, Bhimavaram. A voucher specimen was kept at the Department of Pharmacology, K L College of Pharmacy.

2.2 Extraction and Isolation of the Fractions

2.2.1 Preparation of Plant Extract

The whole plant was dried under shade at room temperature. The shade-dried, coarsely powdered roots (500 g) were successively extracted with petroleum ether (60-80oC) for 7 days to remove fatty matter. The defatted marc was then subjected to soxhlet extraction with 95% methanol to obtain the methanolic extract. The methanolic extract was evaporated under reduced pressure at a low temperature (30oC) to dryness, and brownish-yellow colour extracts of *Biophytum reinwardtii* were obtained[10].

2.2.2 Separation of Active Compounds by Column Chromatography

A cylinder-formed glass column containing a stationary section (silica gel) is encountered slowly from the highest with a liquid solvent (mobile phase) that flows down the column with the assistance of gravity or external pressure applied. This technique is used for the purification of compounds from a mixture. Once the column is prepared, the sample is loaded inside the top of the column. The mobile solvent is then allowed to flow down through the column. The compounds in the mixture have entirely different interactions ability with the stationary section (silica gel), and mobile section, thereby will flow along with the mobile phase at different time intervals or

Table 1. Gradient solvent system used in column chromatography

Gradient solvent system used in column chromatography for the isolation of fractions in *Biophytum reinwardtii* whole plant		
Solvent system	Ratio	Fraction
Hexane	100%	-
Hexane: Ethyl acetate	95: 5	A
Hexane: Ethyl acetate	70: 30	B
Hexane: Ethyl acetate	50:50	C
Only ethyl acetate	100%	D
Only methanol	100%	E

degrees. This means the separation of compounds from the mixture is achieved.

The individual compounds are collected as fractions and analyzed additional for structure elucidation (Table 1).

2.2.3 Preliminary Phytochemical Screening

The methanolic extract was subjected to preliminary phytochemicals for the detection of various constituents.

2.2.4 Animals used in the Study

Healthy adult albino Wistar rats weighing 200-250 grams of Wistar rats were selected for the study. Animals were housed in acceptable cages in uniform healthful conditions and fed with a commonplace pellet diet (Amrul Laboratory ANIMAL Diet) and water ad-lib. Animal studies had the approval of the IACE committee for control and supervision of experiments on animals IAEC-439/Po/01/a/CPCSEA.

3. Experimental design

3.1 Acute Toxicity Studies

Acute toxicity studies were performed according to the organization for economic cooperation and development OECD guidelines 429. Animals were divided into groups (n = 4) and fasted for 4 h with free access to water only. The Hexane and Ethyl Acetate fraction A was administered orally in doses of 5, 50,200 and 2000 mg/kg to different groups of mice and observed over 24 hr., for mortality and physical/behavioural changes[11].

3.2 Dexamethasone-Induced Insulin Resistance in Rats

All rats were weighed before the experiment, group I (normal control) received an equal amount of 1% gum acacia(1ml/kg/p.o), and 30 rats were rendered hyperglycaemic by daily administration of a pre-standardized dose of Dexamethasone (1mg/kg/i.m) for consecutive 7 days and then animals are divided into five groups, each group contain six animals. Group II (dexamethasone control) continued to receive only Dexamethasone and 1% gum acacia(1 ml/kg.po) for the next 15 days. Group III received Pioglitazone (2mg/kg/po) along with Dexamethasone respectively for 15 days. Groups IV and V have treated Dexamethasone along with two different doses of HEMBR 50mg and 100mg/kg/p.o. Respectively for 15 days. Simultaneously two other groups (group VI and VII) of noramohypoglycemic rats were administered with two different doses of HEMBR 50mg and 100mg/kg/p.o., respectively. On the last day, after overnight fasting, all animals are weighed, and blood samples were collected by a retro-orbital puncture for the estimation of glucose and triglycerides. After the collection of blood samples, all animals were sacrificed by cervical dislocation. The assessment of glucose and triglycerides was done by GOD/POD method and GPO/POD methods respectively[12].

3.3 Hepatic Antioxidant Enzyme Assay (Estimation of GSH, SOD and CAT)

Liver samples were dissected out and washed with ice-cold saline immediately to remove as much as blood possible. Now liver homogenate (5%w/v) was prepared in cold 50mM Tris buffer (pH 7.4) using a homogenizer. The prepared homogenate was centrifuged at 5000 rpm for 10 minutes. The supernatant was used for the estimation of GSH, SOD and CAT[13–15].

3.4 Effect of HEMBR on Glucose Uptake in Isolated Rat Hemidiaphragm

Glucose uptake in isolated rat hemidiaphragm was estimated by the method described by Chattopadhyay *et al.* with some modifications. Twelve sets containing graduated test tubes (n = 6) each, were used for the study of non-insulin-assisted and insulin-assisted glucose uptake. The diaphragms were taken out quickly, avoiding traumas and divided into two halves. The hemidiaphragm was rinsed in cold Tyrode solution (without glucose) to remove any blood clots. In a non-insulin assisted glucose uptake study, one hemidiaphragm of each animal from groups I to VI has exposed to 2 ml Tyrode solution with glucose (2000 mg/l) in respective graduated test tubes. In insulin assisted glucose uptake study, the remaining hemidiaphragm of each animal from groups I to VI was exposed to 2 ml Tyrode solution with glucose (2000 mg/l) + insulin (0.25 IU/ml) in respective graduated test tubes. All the graduated test tubes were incubated for 30 min at 37°C in an atmosphere of 95%O_2–5% CO_2 with shaking at 140 cycles per minute. Following incubation, the hemidiaphragm was taken out and weighed. GOD/POD, enzymatic method measured the glucose content of the incubated medium[16]. Glucose uptake was calculated as the difference between the initial and final glucose content in the incubation medium (Table 3).

4. Statistical Analysis

The results were expressed as mean ± SEM and statistically analyzed by ANOVA followed by the Dunnett test, with the level of significance set at $p< 0.05$.

5. Results

Phytochemical studies of Fraction A (Hexane: Ethyl acetate) revealed the Fraction presence of fatty acids, phenolics and flavonoids (Table 2).

5.1 Acute Oral Toxicity Studies

No abnormal behaviour and no mortality observed for HEMBR

5.2 Effects of HEMBR on Plasma Glucose, Serum Triglyceride and Body Weight

In the DEXA-control group, there was a significant increase in plasma glucose level ($p < 0.01$) and serum triglyceride level ($p < 0.01$) when compared with normal control. All Rats treated with DEXA and HEMBR showed a significant decrease (###$p < 0.01$) in the levels of plasma glucose and serum triglyceride when compared with DEXA-control (Figure 1). The Rats treated with DEXA and Pioglitazone showed a significant decrease in plasma glucose level ($p < 0.01$) and serum triglyceride level ($p < 0.01$) when compared with DEXA-control (Figure 2). HEMBR at the dose of 100 mg/kg,p.o., showed marginal hypoglycemia (###$p < 0.05$) when compared with normal control. Whereas a significant decrease in the plasma glucose was observed when compared with DEXA-control, HEMBR at the dose of 50 and 100 mg/kg, p.o., showed a significant reduction ($p < 0.01$) in plasma glucose and triglyceride level. A significant reduction in body weight was observed in the DEXA-control group when compared with the normal control. HEMBR and Pioglitazone treatment significantly inhibited the Dexamethasone-induced decrease in body weight ($p< 0.01$) when compared to DEXA-control (Figure 3). According to

Table 2. Identification of phytochemical constituents

S.No	Phytochemical tests	H:EA (95: 5)	H:EA (70:30)	H:EA (50:50)	EA only	H only	M only
1	Alkaloids	-	-	-	-	-	-
2	Glycosides	-	-	-	-	-	-
3	Tannins	-	-	-	-	-	-
4	Phenols	++	-	-	-	-	-
5	Flavonoids	++	++	-	-	-	-
6	Saponins	-	-	-	-	-	-
7	Steroids	++	++	--	--	--	--

Where (+) Indicates presence, and (-) Indicates absence
H- Hexane, EA-Ethyl acetate, M-methanol

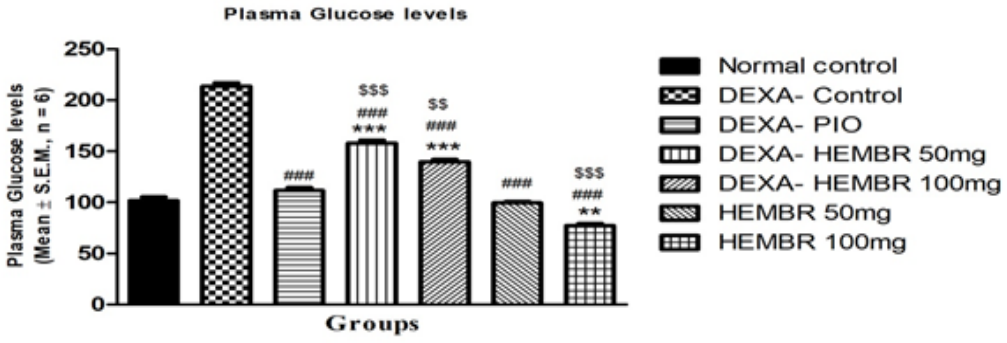


Figure 1. Effect of HEMBR on plasma glucose levels.

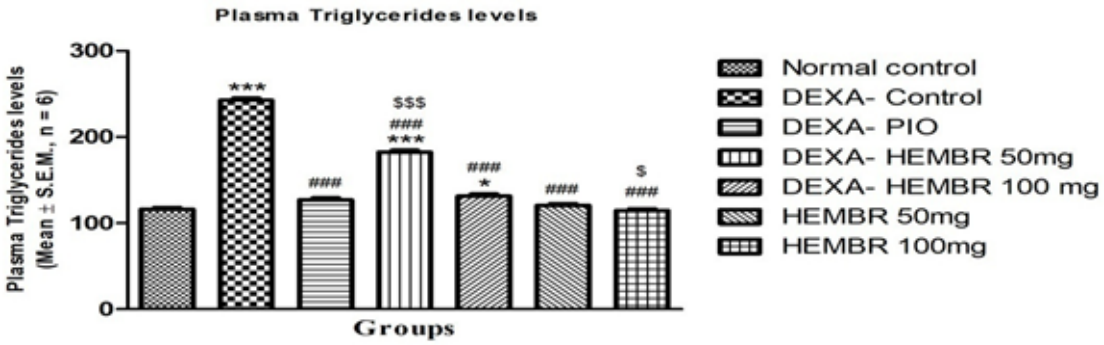


Figure 2. Effect of HEMBR on plasma triglycerides levels.

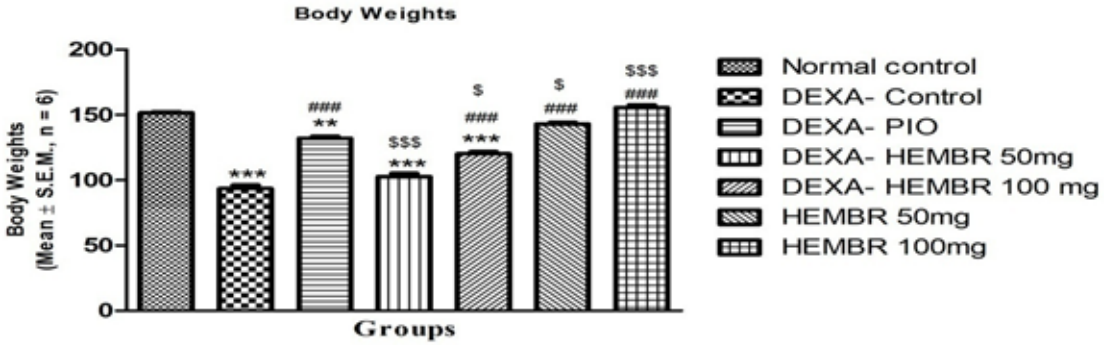


Figure 3. Effect of HEMBR on bodyweight.

the result, it is clear that the HEMBR has a significant effect on DEXA-induced insulin resistance.

All values are expressed in mean ± SEM. Dexamethasone group animals show a high level of plasma glucose when compared to a standard control, PIO group and HEMBR group of animals significantly reduced (###p < 0.05) glucose levels, when compared to Dexamethasone, treated group and only HEMBR group animals do not show any variation in glucose levels when compared to the normal group.

All values are expressed in mean ± SEM. Dexamethasone group animals show a high level of plasma triglycerides levels (***p < 0.01) when compared to a standard control, PIO group and HEMBR group of animals significantly reduced (###p < 0.05) triglycerides levels, when compared to Dexamethasone, treated group and only HEMBR group animals do not show any significant variation in glucose levels when compared to the normal group.

All values are expressed in mean ± SEM. Dexamethasone group animals show decreases in body weight (***p < 0.01) when compared to normal control, PIO group and HEMBR group of animals significantly increased in body weight(###p < 0.05) when compared to the Dexamethasone treated group. Only HEMBR group animals do show significant variation in body weight when compared to the normal group.

5.3 Effects of HEMBR on GSH, SOD and CAT Levels

In DEXA-control group showed a significant decrease (p < 0.01) in GSH, SOD and CAT when compared with normal control, (Figure 4,5,6) whereas a significant increase (###p < 0.05) in the levels of these enzymes was observed in the HEMBR treated groups when compared with DEXA-control group. HEMBR showed a dose-dependent increase in the level of the enzyme. HEMBR at 50 mg/kg, p.o., showed a slight variation in the enzyme level, whereas HEMBR100 mg/kg, p.o., showed a significant increase in the enzyme level.

All values are expressed in mean ± SEM. Dexamethasone group animals show decreased levels of GSH (***p < 0.01) when compared to normal control, PIO group and HEMBR group of animals significantly increased levels of GSH (###p < 0.05) when compared to the Dexamethasone treated group

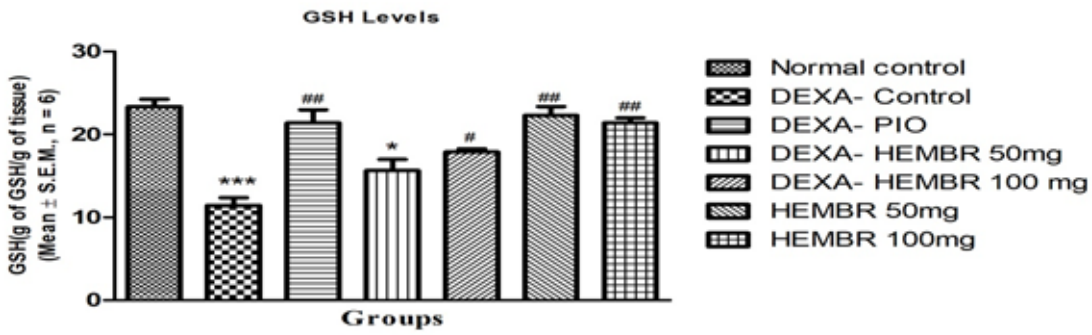


Figure 4. Effect of HEMBR on GSH levels.

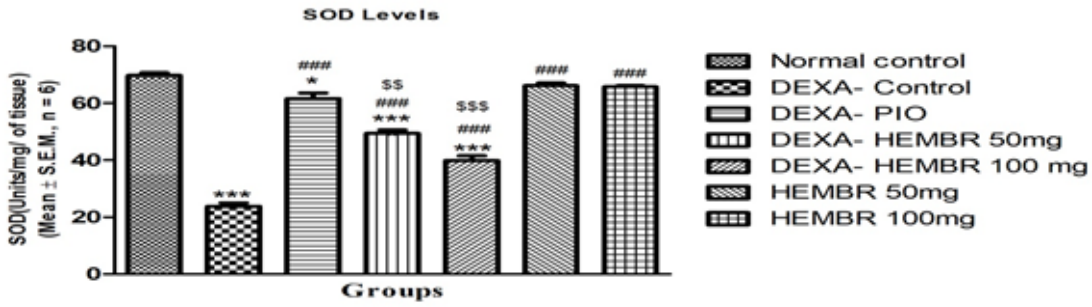


Figure 5. Effect of HEMBR on SOD levels.

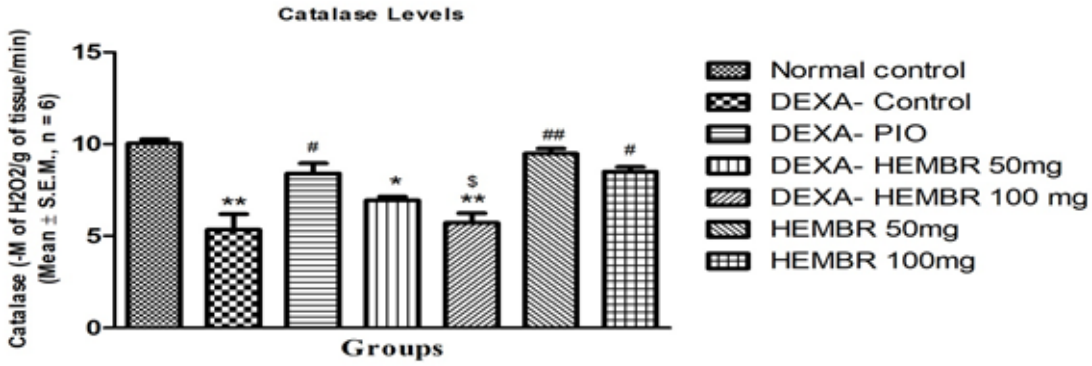


Figure 6. Effect of HEMBR on Catalase levels.

and only HEMBR group animals do not show any significant variation in GSH levels when compared to the normal group.

All values are expressed in mean ± SEM. Dexamethasone group animals show decreased levels of SOD (***p < 0.01) when compared to normal control, PIO group and HEMBR group of animals significantly increased levels of SOD (###p < 0.05) when compared to the Dexamethasone treated group and only HEMBR group animals do not show any significant variation in SOD levels when compared to the normal group.

All values are expressed in mean ± SEM. Dexamethasone group animals show decreased levels of catalase (**p < 0.01) when compared to normal control, PIO group and HEMBR group of animals significantly increased levels of catalase (###p < 0.05) when compared to Dexamethasone treated group and only HEMBR group animals show any significant variation in catalase levels when compared to the normal group.

5.4 Effect of HEMBR on Glucose Uptake in Rats Isolated Hemidiaphragm

Hemi diaphragm of the Rats treated with Dexamethasone

Table 3. Effect of HEMBR on glucose uptake in rats isolated hemidiaphragm

S.No	Groups	Non-insulin assisted glucose uptake mg/g/30min	insulin assisted glucose uptake mg/g/30min
I	Normal control	10.9 ± 0.01	16.2 ± 0.78
II	DEXA- Control	5.15 ± 1.25*	8.23 ± 0.98
III	DEXA- PIO	7.68 ± 0.32	26.23 ± 2.13
IV	DEXA- HEMBR 50mg	8.20 ± 0.42	19.25 ± 1.45
V	DEXA- HEMBR 1000	14.58 ± 0.2**	25.21 ± 0.35***

All values are expressed in sem ±SEM,n = 6, Dexa- Dexamethasone 1 mg/kg.i.m
PIO- Pioglitazone 2mg/kg.p.o, HEMBR- 50 and 100mg/kg.p.o.
*p<0.01 when compared to normal control or normal +Insulin
**p<0.01 when compared to Dexa-control
***p<0.01 when compared with the Dexa +Insulin group

showed a significant decrease ($p < 0.01$) in glucose uptake when compared with normal control. Pioglitazone did not show any significant increase in glucose uptake by Rats isolated hemidiaphragm. HEMBR at higher doses i.e., 50, 100 mg/kg, p.o., showed a significant increase ($p < 0.01$) in glucose uptake when compared with DEXA-control. In insulin-assisted glucose uptake, Pioglitazone showed a significant increase ($p < 0.01$) in glucose uptake when compared with DEXA+ insulin group (Table 3). At dose HEMBR 100 mg/kg, p.o., along with insulin showed a significant increase (###$p < 0.05$) in glucose uptake when compared with DEXA + insulin group.

6. Discussion

In the present study, the effect of HEMBR has been studied for its antidiabetic activity in diabetic animals. Dexamethasone administration at a dose of 1 mg/kg intramuscular resulted in a significant increase in blood glucose (210.3 ± 2.12) and triglyceride level (240.3 ± 0.21). Animals which show blood glucose levels of more than 150 mg/dl were selected for further studies. HEMBR showed a dose-dependent decrease in elevated plasma glucose and triglyceride levels caused by Dexamethasone. The effect of HEMBR on the plasma glucose level and triglyceride level may be due to glucocorticoid antagonism and the presence of other chemical constituents like Flavonoids and phenolic compounds which are also responsible for antihyperglycemic action. HEMBR showed a significant increase in insulin-assisted glucose uptake, which indicates that there was an increase in insulin sensitivity.

Glucocorticoid treatment is known to induce insulin resistance and catabolic states in rats[17]. Pharmacological doses of glucocorticoids caused gene expression in rat adipocyte tissues within 24 h which is followed by complex metabolic changes like hyperleptinemia, resulting in a decrease in food consumption, and a reduction in body weight with enhanced blood glucose and triglyceride levels[18]. As expected, in the present study, the dexamethasone group showed a decrease in body weight, while HEMBR and Pioglitazone treatment inhibited Dexamethasone-induced reduction in body weight and showed a marginal increase in body weight. The effect of HEMBR on the bodyweight may be attributed to the rise in the sensitivity to insulin and the subsequent increase in glucose uptake[19].

Oxidative stress can be generated by hyperglycemia, and for a long time, it has been accused to cause insulin resistance. Insulin resistance induces the release of cytokines like TNF-alpha, IL-8 which leads to the development of oxidative stress in the liver by reducing the mitochondrial levels of Cu/Zn SOD, and glutathione and producing H_2O_2 radicals and leading to an increase in lipid peroxidation. Mitochondria are a significant source for the generation of superoxide radicals[20]. Insulin resistance is associated with an increase in fat accumulation and mitochondrial oxidative stress. In the present study, HEMBR showed a significant increase in the concentration of various antioxidant enzymes, which could be beneficial in countering; hyperglycemia-induced oxidative stress. The fraction of methanolic extract of BR contains flavonoids, and phenolic compounds play a significant role in reducing oxidative stress associated with diabetes, probably by scavenging the

free radicals and preventing the depletion of endogenous antioxidants.

7. Conclusion

According to the findings, HEMBR may be useful in the treatment of insulin resistance due to its antioxidant activity and ability to increase glucose uptake.

8. Acknowledgement

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