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Insulin-sensitizing and antioxidant effects of *Ethulia conyzoïdes* aqueous extract in dexamethasone-induced insulin resistant rats

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Abstract

Rising the prevalence of type 2 diabetes mellitus in sub-saharian Africa has necessitated surveys of antidiabetic medicinal plants. *Ethulia conyzoïdes* is a plant widely used in traditional medicine to treat diabetes. However, the different mechanisms by which it exerts its antidiabetic effects remain unknown. Thus, this study aimed to investigate the effect of *Ethulia conyzoïdes* aqueoux extract on dexamethasone-induced insulin resistance in *Wistar* rats.

Insulin resistance was induced by intraperitoneal injection of dexamethasone (1mg/kg) for 8 days and the animals received simultaneously, orally, distilled water (insulin resistant control group) and, metformin (100 mg/kg) or *Ethulia conyzoïdes* aqueoux extract at doses of 133 and 266 mg/kg. Normal control rats received NaCl 0.9% (intraperitoneal by injection) and distilled water orally. Insulin sensitivity, total cholesterol, triglycerides, transaminases activity and redox status were evaluated.

Results showed a significant reduction of insulin tolerance ($p<0.001$), a drastic increased of transaminase activity ($p<0.05$), hyperlipidemia, and a great potentiation of liver antioxidant enzymes (GSH, SOD and catalase) in insulin resistant control group. *Ethulia conyzoïdes* aqueoux extract markedly improved insulin sensitivity and reversed all the modified parameters.

This study demonstrated the efficacy of *Ethulia conyzoïdes* aqueoux extract to improve insulin sensitivity and manage biochemical disorders induced by insulin resistance. Short term administration of dexamethasone appears to stimulate the first line antioxidant defense in order to counteract oxidative stress, meaning that *Ethulia conyzoïdes* aqueoux extract inhibited free radicals production.

1. Introduction

Insulin resistance (IR) is a condition in which the pancreas is required to secrete more insulin than normal in order to achieve normal blood glucose levels due to reduced sensitivity or responsiveness of tissues to insulin biological activity [1,2]. It is the main cause of type 2 diabetes mellitus (T2DM) development, the most common form of diabetes [3]. IR has significant effects on skeletal muscle, adipocytes, and liver tissues which are the main targets of intracellular glucose transport as well as glucose and lipid metabolism [4]. It causes impaired glycogen synthesis and protein catabolism in skeletal muscles and inhibits lipoprotein lipase activity in adipocytes leading to an increased release of free fatty acids; additionally, it leads to impaired glucose output and fatty acid metabolism leading to increased triglyceride content and VLDL secretion from liver [5,6,7]. IR is also associated with oxidative stress which has been recently recognized as a key mechanism in its pathophysiology [8,9,10].

In addition to T2DM, there is a large spectrum of diseases associated with IR such as obesity, cardiovascular disease, nonalcoholic fatty liver disease, metabolic syndrome, and polycystic ovary syndrome, revealing its multifactorial character and high prevalence. According to Goh et al. [11], the worldwide prevalence of IR ranges from 15.5% to 46.5 %. So, finding an adequate treatment for IR is a great advance in medicine because it permits to limit the occurrence and severity of T2DM and the other associated diseases. Lifestyle changes, dietary approaches and chemical agents are commonly used, but IR and its consequences on health remain a major public health problem. Indeed, due to the socio-economic conditions of most populations, especially those of rural areas, access to these different treatments is not always easy. Moreover, most drugs have a lot of side-effects such as hypoglycemia caused by sulphonylureas and insulin [12,13], lactic acidosis and gastrointestinal disorders due to metformin [14,15]. Alternative to these synthetic agents, plants are used in several traditional medicine. They provide a potential sources of phytoconstituents responsible for a diversity of beneficial effects on health (improvement of insulin sensitivity, enhancement of antioxidant defense, protection of β-cell damage, regulation of insulin signaling pathway [16]), with low side-effects.

Ethulia conyzoïdes Linn (Asteraceae) is an herb that grows up to 1.5 m high around wet grass land and river side [17]. The leaves are used as therapy for cancers in Madagascar [17] and south western Nigeria [18]. It has been experimentally demonstrated that *E. conyzoïdes* has antioxidant activity [19,20], anti-helminthic and antibacterial properties [21,22]. In Cameroon, the whole plant is used as antidiabetic in traditional medicine, but no scientific study has been done to date to validate its traditional use and determine its mechanism of action In this study, we evaluated the effects of *Ethulia conyzoïdes* aqueoux extract (ECA) on dexamethasone-induced insulin resistance in rats.

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2. Materials and Methods

2.1. Chemicals

D-glucose was purchased from Edu-Lab Biology Kit (Bexwell, UK). All other chemicals (analytical grade) were available commercially.

2.2. Plant material

The whole plant of *E. conyzoïdes* was collected from Dschang, Cameroon in June 2020 and authenticated at the National Herbarium of Cameroon, by comparison with the voucher specimen (N° 19048/SRFK).

2.3. Extraction of plant material

The whole plant of *E. conyzoïdes* was washed down with tap water appropriately and then shade dried and grinded into fine powder. The aqueous extract was then obtained by decoction of 500g of fine powder into 5L of distilled water for 10 min. This was followed by filltration with a filter paper whatmann N°1, and the filtrate was evaporated in the oven at 45°C. The crude extract of *E. conyzoïdes* was weighed (60.62g) and kept cool. The therapeutic dose (133mg/kg) was determined according to the tradipratician recommendations. The second dose administered (266mg/kg) was obtained by multiplying the therapeutic dose by two.

2.4. Experimental animals

Male *Wistar* albino rats weighing 200 to 250 g were used for this experiment. They were raised at the animal house of the Department of Animal Biology at the University of Dschang in a natural temperature and luminosity, with a free access to water and standard laboratory food.
All experiments were conducted in accordance with the ethical guidelines for animal use and care as described by the law 2010/63/EU of the European Parliament on the protection of animals used for scientific purposes.

2.5. Induction of insulin resistance and treatment

Insulin resistance was induced by intraperitoneal injection of dexamethasone at the dose of 1mg/kg for 8 days [23]. During these 8 days, animals were treated as follows.
Group I: normal control received NaCl (0.9%) + distilled water.
Group II: insulin resistant control received dexamethasone + distilled water.
Group III: dexamethasone + metformin (100mg/kg).
Group IV: dexamethasone + aqueous extracts of *E. conyzoïdes* 133 mg/kg.
Group V: dexamethasone + aqueous extracts of *E. conyzoïdes* 266 mg/kg.

All the treatments were admistered orally, one hour after dexamethasone or NaCl injection. Fasting blood glucose level was measured at the last day of treament and insulin tolerance test was performed. Then, blood was collected by catheterization of abdominal artery under anesthesia with diazepam (10mg/kg) and ketamine (50mg/kg) and serum was obtained by centrifugation at 3000 rpm for 15 min. Immediately after blood collection, liver was removed, cleaned with saline solution (0.9%), and weighed for relative livers' weight (RLW) determination; then used for estimation of oxidative stress parameters.

2.6. Evaluation of the insulin sensitivity

Insulin sensitivity was evaluated by insulin tolerance test and triglyceride glucose (TyG) index. The insulin tolerance test was performed as described by Wuyt et al. [24]: after 6 hours fasting, the rats received subcutaneous injection of insulin (1UI/kg of BW), then blood glucose was estimated in the blood collected at the tail vein of rats at 0, 30, 60, 90, and 120 min, using the ACCU-CHEK Active glucometer. The TyG index was calculated as Ln [triglycerides (mg/dl) x glucose (mg/dl)/2] [25].

2.7. Evaluation of serum lipids and liver function

Total cholesterol (TC), triglycerides (TG), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were estimated in the serum using IMMESCO brand kits, according to the manufacturer's instructions.

2.8. Evaluation of oxidative status

Liver tissues were homogenized in Tris buffer and samples were centrifuged at 3000 rpm for 15 min. Supernatants were used to evaluate the amount of malondialdehyde (MDA) by the method of Agbor et Odetola [26] and measure the antioxidant enzymes activity: superoxide dismutase (SOD) by the modified method of Dimo et al. [27], glutathione reductase (GSH) by the modified method of Sehirli et al. [28], and catalase (CAT) by the method of Dimo et al. [27]

2.9. Statistical analysis

Data were analyzed using GraphPad Prism version 8.4.2 and presented as Mean ± Standard Error of Mean (SEM). One-way Analysis of Variance (ANOVA) followed by Tukey's post hoc test or two-way ANOVA followed by Bonferroni's post hoc test were used to compare differences between means. Differences were considered statistically significant at $p < 0.05$.

3. Results

3.1. Effects of *Ethulia conyzoïdes* on body and liver weight

Table I shows the main body weight and relative liver weight of rats at the end of treatment. It appears that in insulin resistant control group (Group II), body weight significantly decreased ($p<0.001$) whereas liver weight significantly increased ($p<0.0001$) compared to normal control group (Group I). Metformin and ECA did not corrected body weight loss in rats; however, *E. connyzoïdes* showed a non-significant decrease in overall liver weight gain compared to insulin resistant control.

Table1: Body weight and relative liver weight of insulin resistant rats treated with *Ethulia conyzoïdes*

	Body weight	Relative liver weight
Group I	256.67 ± 9.79	2.79 ± 0.08
Group II	214.83 ± 4.76***	3.42 ± 0.15****
Group III	204.83 ± 5.79****	3.39 ± 0.22
Group IV	208.67 ± 4.15****	3.12 ± 0.17
Group V	202.17 ± 4.69****	3.24 ± 0.17

***p<0.001; ****p<0.0001 compared to group I. *n* = 6; data are presented as mean± SEM. Group I: normal control; Group II: insulin resistant control; Group III: Dexamethasone + Metformin (100mg/kg); Group IV: dexamethasone + aqueous extract of *E. conyzoïdes* (133 mg/kg); Group V: dexamethasone + aqueous extract of *E. conyzoïdes* (266 mg/kg).

3.2. Effects of *Ethulia conyzoïdes* on insulin sensitivity

As shown in Fig. 1, analysis of data indicates that dexamethasone significantly reduced insulin tolerance, in addition, it markedly increased TyG index compared to normal control group. In contrast, metformine and ECA administration significantly improved insulin tolerance and at the same time reduced TyG index with the most significant effect at the dose of 133 mg/kg ($p<0.0001$) compared with insulin resistant group.

3.3. Effects of *Ethulia conyzoïdes* on glycemia, serum lipids and liver function

Table 2 reveals that induction of insulin resistance resulted in a significant increase of serum levels of TC, TG, ALT and AST compared with normal rats ($p<0.05$; 0.001). Metformin and ECA significantly reduced these parameters compared to insulin resistant group. Blood glucose level did not change in all the groups compared to normal control.

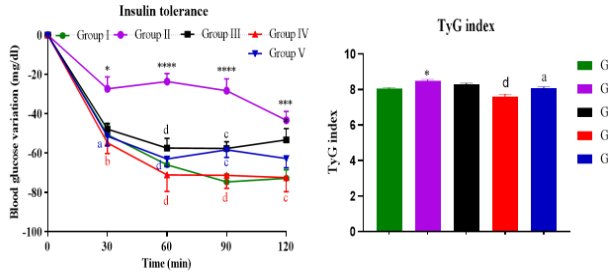

Figure 1: Effects of aqueous extract of *Ethulia conyzoïdes* on insulin sensitivity in dexamethasone induced insulin resistant rats during 8 days of treatment

*p< 0.05; ***p<0.001; ****p<0.0001 compared to group I; [a]p< 0.05; [b]p<0.01; [c]p<0.001; [d]p<0.0001 compared to group II. *n* = 6; data are presented as mean± SEM. Group I: normal control; Group II: insulin resistant control; Group III: Dexamethasone + Metformin (100 mg/kg); Group IV: dexamethasone + aqueous extract of *E. conyzoïdes* (133 mg/kg); Group V : dexamethasone + aqueous extract of *E. conyzoïdes* (266 mg/kg).

Table 2: Glycemia, lipidemia and hepatic transaminase activity of insulin-resistant rats treated with *Ethulia conyzoïdes*

Groups	Glycemia (mg/dl)	Serum lipids (mg/dl)		Liver function tests (U/L)	
		TC	TG	ALT	AST
Group I	88.17 ± 2.96	50.21 ± 2.16	72.27 ± 5.12	36.38 ± 1.84	80.22 ± 5.68
Group II	78.33 ± 4.34	65.66 ± 5.04*	126.6 ± 10.43***	47.82 ± 3.43*	102.80 ± 2.54*
Group III	84.50 ± 4.00	44.07 ± 1.08c	96.74 ± 6.05	34.77 ± 2.88[b]	79.93 ± 6.65[a]
Group IV	75.67 ± 3.45	45.96 ± 3.08[b]	55.45 ± 7.09[d]	27.55 ± 2.52[d]	85.89 ± 2.31
GroupV	77.67 ± 3.88	48.00 ± 2.88[b]	85.86 ± 9.72[a]	23.43 ± 1.24[d]	74.87 ± 4.43[b]

*p< 0.05; ***p<0.001 compared to group I; [a]p< 0.05; [b]p<0.01; [c]p<0.001; [d]p<0.0001 compared to group II. *n* = 6; data are presented as mean± SEM. Group I: normal control; Group II: insulin resistant control; Group III: Dexamethasone + Metformin (100mg/kg); Group IV: dexamethasone + aqueous extract of *E. conyzoïdes* (133 mg/kg); Group V: dexamethasone + aqueous extract of *E. conyzoïdes* (266 mg/kg).

3.4. Effects of *Ethulia conyzoïdes* on oxidative stress parameters

Liver SOD, GSH and CAT levels significantly raised (p<0.05; p<0.01) in insulin resistant rats compared to normal rats. In groups treated with ECA, SOD and CAT levels drastically reduced (p<0.01 to p<0.0001) compared to insulin resistant control group. In addition, both doses of extract caused a non-significant decline of GSH level compared to insulin resistant control group. However, it should be noted that there was not significant change of MDA level in all groups of rats compared to normal rats (Table 3).

Table 3: Hepatic oxidative stress parameters of insulin-resistant rats treated with aqueous extract of *Ethulia conyzoïdes*

Groups	MDA (ug/mg of liver)	SOD (unite/mg of proteins)	GSH (mg/g of proteins)	CAT (H_2O_2/mg of proteins/min)
Group I	0.58 ± 0.05	36.38 ± 1.84	29.03 ± 1.59	1.44 ± 0.10
Group II	0.53 ± 0.03	47.82 ± 3.43*	38.57 ± 2.64*	4.08 ± 0.32****
Group III	0.51 ± 0.04	34.77 ± 3.64[a]	37.45 ± 1.90	3.06 ± 0.33
Group IV	0.52 ± 0.03	27.55 ± 2.52[c]	33.01 ± 2.57	2.53 ± 0.16[b]
GroupV	0.50 ± 0.03	23.43 ± 1.24[d]	33.59 ± 0.73	1.56 ± 0.28[d]

*p< 0.05; ****p<0.0001 compared to group I; [a]p< 0.05; [b]p<0.01; [c]p<0.001; [d]p<0.0001 compared to group II. *n* = 6; data are presented as mean± SEM. Group I: normal control; Group II: insulin resistant control; Group III: Dexamethasone + Metformin (100mg/kg); Group IV: dexamethasone + aqueous extract of *E. conyzoïdes* (133 mg/kg); Group V : dexamethasone + aqueous extract of *E. conyzoïdes* (266 mg/kg).

4. Discussion

The present study investigates the possible protective effects of ECA on insulin resistance induced by dexamethasone in rats. As shown by the literature and previous studies [23,29], intraperitoneal injection of dexamethasone effectively generated insulin resistance in normal rats as evidenced by decreased insulin tolerance, increased TyG index, hypercholesterolemia and hypertriglyceridemia.

Following the treatment with ECA and metformin, insulin tolerance increased significantly and TyG index reduced. Studies have shown that TyG index is an effective screening tool in predicting IR [30,31]. Thus, the decrease in the TyG index suggests that the plant extract has improved insulin sensitivity as indicated by the insulin tolerance test presented in figure 1. ECA also reversed hypercholesterolemia and hypertriglyceridemia caused by dexamethasone (Table 2). Hyperlipidemia in the insulin resistance condition is due to lowering lipoprotein lipase activity and increasing activity of hormone-sensitive adipose tissue lipase which leads to an increase in fatty acids mobilization from adipocytes and an increase in hepatic synthesis of triglycerides released into the bloodstream as VLDL cholesterol [32]. The hypolipidemic effect of ECA could be associated to it insulin sensitizing action, thus restoring the activity of these enzymes involved in lipid metabolism.

As expected in the present study, dexamethasone group showed reduction in body weight (Table 1). It has been shown that dexamethasone causes muscle protein degradation [33] and inhibition of muscle protein synthesis [34], leading to skeletal muscle atrophy which could, according to Fofie et al. [35], justifying body weigh lost. However, ECA did not prevent the weigh lost observed in dexamethasone control group, suggesting that the extract did not antagonize the mechanism by which dexamethasone induces muscle wasting in rats.

Liver weight and transaminase activity (ALT and AST) of dexamethasone treated rats were significantly increased as compared to control group (Tables 1,2). This is not surprising giving the fact that several studies have reported the harmful effects of dexamethasone-induced insulin resistance in the liver. Indeed, insulin resistance may enhance fat accumulation by increasing free fatty acid delivery and by the effect of hyperinsulinemia to stimulate anabolic process [36]. Lipid accumulation is one of diverse causes of liver weight gain [37]. Furthermore, it has been shown that elevated levels of alanine and aspartate aminotransferases are associated with IR [38,39]. ALT and AST are hepatic enzymes whose release into the bloodstream is considered to provide strong evidence for hepatic necrosis [40]. So the decrease in liver weigh and transaminase activity observed in treated groups could be attributed to the ability of ECA to increase liver insulin sensitivity thereby reducing fat accumulation and cell damages.

The results from this study showed that 8-days administration of dexamethasone at dose of 1 mg/kg has consistently potentiated antioxidant defenses of animals (Table 3). Serum levels of SOD, CAT and GSH significantly increased in dexamethasone control group as compared to control whereas MDA level did not change. SOD, CAT and GSH are first line defense antioxidants acting against reactive oxygen species (ROS). SOD scavenges superoxide radicals to H2O2 and thus provide protection against the deleterious effects of radicals. H2O2 accumulated by this reaction leads to the formation of hydroxyl radicals which are scavenged by CAT and GSH [41,42]. So, their high levels in these animals clearly demonstrate that dexamethasone promoted the ROS production in the liver, leading to the activation of the first line antioxidant defense. This antioxidant activity could explain the unchanged level of MDA, the end product of lipid peroxidation. Thus, the restored redox status in treated animals could be due the capacity of ECA to prevent ROS production by dexamethasone.

5. Conclusion

In conclusion, aqueous extracts of *E. conyzoïdes* was found to be useful in the management of insulin resistance owing to its ability to increase

insulin sensitivity, reduce hyperlipidemia, and prevent free radicals production and liver damages.

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