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Efficacy of *Emilia coccinea* aqueous extract on inhibition of α-amylase enzyme activity and insulin resistance in dexamethasone treated-rats

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ABSTRACT

Background: Diabetes mellitus is one of the most common chronic metabolic diseases throughout the world, characterized by hyperglycemia and insulin resistance. The purpose of this study was to evaluate the effects of aqueous extract of *Emilia coccinea* (AEEC) leaves on dexamethasone-induced insulin resistance in rats and on *in vitro* α-amylase enzyme activity.

Methods: Insulin resistance was induced by intraperitoneal injection of dexamethasone (1 mg/kg) for 8 days in rats. The animals were concomitant received extracts at doses of 107.5; 215; 430 mg/kg for this period. At the end of the treatment, blood glucose level, lipid profile, transaminases, triglyceride glucose (TyG) index, body mass and relative organ weight were evaluated.

Results: The results showed that AEEC inhibits α-amylase enzyme with an IC_{50} of 34.10 μg/ml *in vitro*. AEEC significantly reduced blood glucose level, triglycerides, TyG index, total and LDL cholesterol, liver weight and increased HDL cholesterol. Moreover, it reduced ALAT and ASAT activity. These parameters were strongly modify by dexamethasone.

Conclusion: AEEC plays antidiabetic roles by ameliorating insulin resistance and reducing postprandial blood glucose level through α-amylase enzyme inhibition.

1. Introduction

Diabetes mellitus is (DM) is one of the most common chronic metabolic diseases throughout the world [1]. It is characterized by hyperglycemia and glucose intolerance which bring about defects of insulin secretion or insulin's action to boost glucose uptake [2]. The gradual progression of this disease affects organs of the body, and serious complications appear after onset of diabetes. It is the most prevalent and rapid-growing worldwide problem and arise as a huge health and socioeconomic burden [3,4]. The International Diabetes Federation estimated the global prevalence of diabetes at 8.4% in 2017 and is expected to increase to 9.9% in 2045 [5]. Type 2 diabetes mellitus (T2DM) accounts for about 90% of diabetes cases and is mainly characterized by insulin resistance and hyperglycemia. So, improving insulin resistance and hyperglycemia may provide a therapeutic strategy for controlling T2DM.

Several modern approaches are used to controlling diabetes such as intensive lifestyle interventions and antidiabetic drugs. However, these different treatments have limitations including a socio-economic context not conducive to diabetic diet, difficulty in distributing drugs often inaccessible to many populations, adverse effects of drugs and the complexity of treatment that combines several classes of medications with the consequent increase in adverse effects [6]. As a result, herbal medicine very rapidly became a therapeutic alternative because it is very effective, available and has fewer side effects.

Emilia coccinea is a plant from the Cameroonian pharmacopoeia, used in traditional medicine to solve many health problems such as diabetes, eye problems, ever, convulsions in children, ulcers, inflammatory diseases [7]. Despite these interesting pharmacological effects, no study has report the effects of *E. coccinea* on insulin resistance and α-amylase enzyme.

The aim of this study was to investigate the effects of aqueous extract

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of *E. coccinea* on insulin resistance induce by dexamethasone in rats and on α-amylase enzyme inhibition.

2. Material and methods

2.1. Chemicals and drugs

Acarbose, α-amylase and 3,5-dinitrosalicyli acid (DNSA) were purchased from Sigma Aldrich, St. Louis, USA. D-glucose, starch and sodium chloride (NaCl) were purchased from Edu-Lab Biology Kit (Bexwell, UK). All others chemicals and drugs were of analytic grade available commercially.

2.2. Plant material

Leaves of *Emila coccinea* were collected in Dschang (West-Cameroon) and authenticated at the National Herbarium of Cameroon by comparison to the voucher specimen registered at number N°19052/SRF/CAM. Leaves were shade-dried, then powdered with a mechanical grinder to obtain a fine powder.

2.3. Preparation of aqueous extract

Three hundred grams (300 g) of powder of *E. coccinea* were macerated in 3 L of distilled water for 72 h at room temperature, with constant stirring. The mixture was then filtered with a filter paper whatmann N°1. The filtrate was evaporated in oven at 40 °C. The percentage yield of the extract was 17, 08%. The crude extract was dissolved in distilled water according to the doses to be administered.

2.4. Animals

Male albino Wistar rats weighing between 180 and 250 g and aged 8–12 weeks age were used for this study. They were raised at the animal house of the Department of Animal Biology at the University of Dschang-(Cameroon) at natural temperature and luminosity. They were given standard laboratory food and water ad libitum.

All experiments were conducted in compliance with ethical guide for care and use of laboratory animals. The animals were treated in accordance with the internationally accepted standard ethical guidelines for laboratory animal use and care as described in European Community Guidelines.

2.5. In vitro α-amylase inhibitory assay

The α-amylase inhibition assay was performed using the 3,5-dinitrosalicilic acid (DNSA) method [8]. A volume of 500 µl of aqueous extract of *E. coccinea* at different concentrations (1, 3, 10, 30, 100 and 300 µg/mL) were added to 500 µl of tris buffer (0.20 mM, PH = 7) containing 500 µl of alpha amylase solution (0.5 mg/mL). The mixture was incubated at 25 °C for 20 min. Subsequently, 250 µL of 1% starch solution contained in the tris sodium buffer (0.02 M, pH = 7) was added and the reaction mixtures were incubated at 25 °C for 10 min. The reaction was stopped by adding 2 mL of 3,5-dinitrosalicylic acid colored reagent, then the test tubes were incubated in a boiling water bath at 100 °C for 5 min and cooled to room temperature. The reaction mixture was diluted by addition of 10 ml of distilled water and the absorbance was read at 540 nm. Acarbose was used as positive control. The experiments were repeated four times. The percentage inhibition was calculated according to the formula:

Inhibition (%) = A540 control - A540 sample / A540 control * 100

2.6. Oral glucose tolerance test

Oral glucose tolerance test was performed with 30 overnight fasted (14 h) rats divided into five groups of six animals each. Group 1 received distilled water, group 2 received metformin at dose of 100 mg/kg body weight (bw), group 3, 4 and 5 were treated with aqueous extract of *E. coccinea* (AEEC) at respective doses of 107,5, 215, and 430 mg/kg bw. One hour after administration of different treatments, D-glucose (3 g/kg bw) was orally administrated to all the rats. Blood glucose was estimated in the blood collected at the tail vein of rats using the ACCU-CHEK Active glucometer. It was recorded before the administration of different substances and at 30, 60, 90, and 120 min after D-glucose treatment.

2.7. Dexamethasone-induced insulin resistance

Insulin resistance was induced by intraperitoneal injection of dexamethasone (1 mg/kg) for 8days as describe by Wego et al. [9]. Thirty-six (36) fasting rats were weighed and divided into six groups of six animals each. . Group 1 served as normal control and received per os (*p.o.*) distilled water and intraperitoneal injection of NaCl (0.9%); group 2 served as insulin resistant control and received distilled water *p.o.* and intraperitoneal injection of dexamethasone; group 3 served as positive control and received metformin (100 mg/kg, *p.o.*) and dexamethasone injection; groups 4, 5 and 6 were treated with AEEC at respective doses of 107,5 215, and 430 mg/kg, *p.o.* plus dexamethasone injection. Blood glucose and body weight were evaluated the first and last day of the treatment.

On the 9th day, animals were anesthetized and blood was collected by catheterization of abdominal artery. Thereafter, blood was centrifuged at 3000 rpm for 15 min and serum was separated for the estimation of lipid profile and transaminases (ASAT and ALAT) activities using commercial standard diagnostic kits. Immediately after blood collection, liver was removed and weighed for relative liver' weight determination. The TyG index was calculated as Ln [triglycerides (mg/dl) x glucose (mg/dl)/2] derived from previous studies [10,11].

2.8. Data analysis

All the results were expressed as mean ± SEM (standard error of mean). Data were analyzed using one-way ANOVA followed by Tukey's post-test (ALAT, ASAT, lipid, and protein levels) and two-way ANOVA followed by Bonferroni's post-test (blood glucose variation and body weight) using Graph Pad Prism version 5.03. $p < 0.05$ was considered significant. The concentration that caused 50% of inhibition (IC_{50}) was calculated using nonlinear regression model.

Table 1
Percentage of inhibition of AEEC and acarbose on α-amylase enzyme.

Concentration (µg/ml)	Percentage of inhibition	
	AEEC	Standard (Acarbose)
1	8.96 ± 0.48	23.01 ± 0.58
3	13.72 ± 0.58	36.63 ± 0.45
10	16.21 ± 0.62	44.05 ± 0.43
30	20.64 ± 0.69	49.65 ± 0.28
100	24.39 ± 1.12	52.67 ± 0.53
300	31.12 ± 1.01	57.75 ± 0.22

AEEC: aqueous extract of *Emilia coccinea*.

Table 2
Effective inhibitory concentration of AEEC and acarbose on α-amylase enzyme.

	AEEC	Acarbose
IC_{50} (µg/mL)	34.10	2.96

AEEC: aqueous extract of *Emilia coccinea*; IC_{50}: Inhibitory concentration.

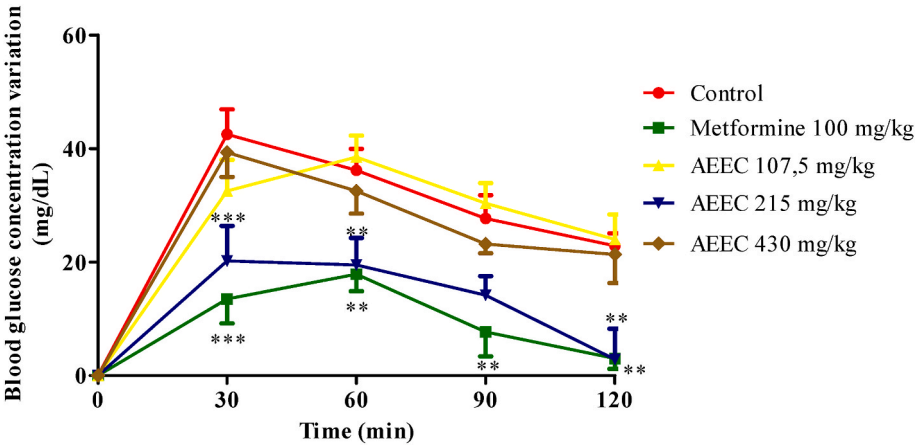

Fig. 1. Effects of aqueous extract of *Emilia coccinea* on postprandial hyperglycemia induced by D-glucose in normoglycemic rats.
AEEC: aqueous extract of *Emilia coccinea*. **p < 0.01; ***p < 0.001 compared to control group. $n = 6$; data are presented as mean ± SEM.

Table 3
Effects of aqueous extract of *Emilia coccinea* on body weight and relative liver weight of insulin resistant rats.

	Body weight	Relative liver weight
Normal control	284.33 ± 6.46	2.76 ± 0.29
Dex control	214.50 ± 2.57***	5.58 ± 0.18***c
Dex + Metformin (100 mg/kg)	253.33 ± 11.78	3.79 ± 0.27***c
Dex + AEEC (107.5 mg/kg)	228.50 ± 22.93**	4.63 ± 0.56***c
Dex + AEEC (215 mg/kg)	267.50 ± 3.27b	3.045 ± 0.041c
Dex + AEEC (430 mg/kg)	238.40 ± 14.92*	4.34 ± 0.28***c

AEEC: aqueous extract of *Emilia coccinea*; Dex: dexamethasone. *p < 0.05; **p < 0.01; ***p < 0.001 compared to normal control group; ^{b}p < 0.01; ^{c}p < 0.001 compared to dexamethasone control group. $n = 6$; data are presented as mean ± SEM.

3. Results

3.1. In vitro α-amylase inhibitory activity

As presented in Table 1, aqueous extract of *E. coccinea* and acarbose has produced a concentration-dependant inhibitory effect on α-amylase enzyme *in vitro*. The IC_{50} values were 34.10 μg/ml for extract and 2.96 μg/ml for acarbose (Table 2).

3.2. Effects of aqueous extract of Emilia coccinea on glucose tolerance test in normal rats

Fig. 1 reveals that from the 30th min, aqueous extract of *E. coccinea* (215 mg/kg) and metformin (100 mg/kg) significantly reduced (p < 0.01; p < 0.001) postprandial hyperglycemia induced by oral administration of D-glucose (3 g/kg). Extract at doses of 107.5 mg/kg and 430 mg/kg had no significant effect on postprandial glycemia.

3.3. Insulin sensitizing effects of Emilia coccinea aqueous extract on dexamethasone-treated rats

3.3.1. Effects on body weight and relative liver weight

Results from Table 3 show that dexamethasone significantly reduced (p < 0.001) body weight and significantly increased (p < 0.001) liver weight of rats after 8 days of administration compared to normal control group. Metformin (100 mg/kg) and aqueous extract of *E. coccinea* protected the rats against these alterations, especially the extract at dose of 215 mg/kg which significantly increased (p < 0.01) body weight and significantly decreased (p < 0.001) liver weight of rats compared to dexamethasone control group.

3.3.2. Effects on biochemical parameters

Effects of aqueous extract of *E. coccinea* on biochemical parameters of insulin resistant rats are presented in Table 4. It should be noted that dexamethasone significantly altered (p < 0.001) biochemical

Table 4
Effects of aqueous extract of *Emilia coccinea* on biochemical parameters of insulin resistant rats.

Biochemical parameters	Normal control	Dex control	Dex + Metformin (100 mg/kg)	Dex + AEEC (107.5 mg/kg)	Dex + AEEC (215 mg/kg)	Dex + AEEC (430 mg/kg)
Glycemia (mg/dl)	81.50 ± 3.01	120.33 ± 3.83***	84.66 ± 3.49c	73.83 ± 6.53c	74.83 ± 4.72c	77.33 ± 3.20c
Total cholesterol (mg/dl)	66.71 ± 1.36	98.49 ± 7.51***	53.79 ± 1.11c	73.95 ± 1.00c	59.47 ± 1.72c	67.84 ± 3.55c
Triglycérides (mg/dl)	70.59 ± 0.59	125.00 ± 5.82***	86.03 ± 2.620c	73.29 ± 5.99c	71.82 ± 6.5359c	92.26 ± 1.30*c
Cholestérol HDL (mg/dl)	26.16 ± 2.83	8.95 ± 1.46**	15.22 ± 3.07	20.04 ± 3.57	15.19 ± 2.91	18.75 ± 3.67
Cholestérol LDL (mg/dl)	26.44 ± 2.73	64.54 ± 8.03***	21.37 ± 3.55c	39.25 ± 2.15b	29.91 ± 1.96c	30.63 ± 4.32c
ALAT (U/L)	71.39 ± 1.21	150.3 ± 10.23***	76.45 ± 4.34c	84.43 ± 2.57c	58.91 ± 3.98c	71.49 ± 1.62c
ASAT (U/L)	61.29 ± 1.29	110.20 ± 10.89***	57.54 ± 5.24c	73.28 ± 3.46b	76.55 ± 2.874b	76.04 ± 5.65b
TyG index	7.96 ± 0.03	8.91 ± 0.05***	8.19 ± 0.05c	7.86 ± 0.10c	7.86 ± 0.06c	8.17 ± 0.03c

AEEC: aqueous extract of *Emilia coccinea*; Dex: dexamethasone; TyG index: triglyceride glucose index. *p < 0.05; **p < 0.01; ***p < 0.001 compared to normal control group; ^{b}p < 0.01; ^{c}p < 0.001 compared to dexamethasone control group. $n = 6$; data are presented as mean ± SEM.

parameters by increasing blood glucose level, total and LDL cholesterols, triglycerides, TyG index, ALAT, ASAT, and by decreasing HDL cholesterol and total proteins. It also emerges from this table that aqueous extract of *E. coccinea* and metformin produced a significant ($p < 0.001$) hypoglycemic effect in treated rats compared to insulin resistant rats. Extract and metformin also significantly reduced ($p < 0.01$; $p < 0.001$) levels of total cholesterol, LDL cholesterol, triglycerides, TyG index and transaminases activity and increased ($p < 0.01$; $p < 0.001$) levels of HDL cholesterol and total proteins compared to dexamethaxone control group.

4. Discussion

Type 2 diabetes is an endocrine disease, which accounts for 9% of deaths worldwide. The aim of oral therapy is to reach normoglycemia to prevent later complications [12]. Among glucose-lowering medications, α-amylase inhibitors and insulin sensitizers are frequently used. So, the aim of the present study was to evaluate the effects of aqueous extract of *E. coccinea* on α-amylase enzyme and dexamethasone-induced insulin resistance in rats.

α-amylase is a key enzyme for carbohydrate digestion which catalyzes the hydrolysis of α-1,4-glucosidic linkages of polysaccharide such as starch and glycogen. Inhibition of α-amylase in the digestive tract of human retards digestion of polysaccahrides and therefore can be important strategy in the management of postprandial blood glucose level in diabetic patients [13,14]. Reducing postprandial hyperglycemia is important given the fact that it can help in reducing advanced glycation end-products (AGEs) formation, a metabolite which has been identified as a major risk factor for cardiovascular complications in diabetic patients [15]. In this study, aqueous extract of *E. coccinea* considerably inhibited the α-amylase enzyme activity although its effect was less than that of acarbose (Tables 1 and 2). This indicates that *E. coccinea* can prevent postprandial hyperglycemia; this effect was confirmed by oral glucose tolerance test in normal rats which showed that aqueous extract of *E. coccinea* at dose of 215 mg/kg significantly reduced the postprandial blood glucose level compared to control group (Fig. 1). Phenols and flavonoïds may account for α-amylase inhibitory activity observed. Several studies have demonstrated that these compounds possess high inhibitory potential toward α-amylase enzyme activity [16–19]. The phytochemical studies carried out by Obinna et al. [20] have revealed the significant amounts of flavonoids (0.90 mg/100 g) and phenols (0.89 mg/100 g) in the *E. coccinea* leaves.

Insulin sensitizers are antidiabetic drugs that act by improving the sensitivity of peripheral tissues to insulin. Their mechanisms include reduction of hepatic glucose production and increase in insulin-mediated glucose utilization in skeletal muscle and adipocytes. Insulin sensitizing effect of *E. coccinea* was tested on the model of dexamethasone-induced insulin resistance in rats. Dexamethasone is a synthetic glucocorticoid widely used for the treatment of inflammation, autoimmune disorders, and preventing rejection in organ transplant recipients [21]. Despite their therapeutic action, chronic administration of glucocorticoids may lead to hyperglycemia, dyslipidemia, glucose intolerance, insulin resistance, and imbalance in lipid metabolism [22]. As expected in the present study, 8-days administration of dexamethasone at dose of 1 mg/kg caused hyperglycemia and dyslipidemia; it also induced a significant increase of TyG index (Table 4). Numerous studies have shown that TyG index is a useful indicator of insulin resistance [11, 23–26]. *Emilia coccinea* treatment generated a reduction of blood glucose level, triglycerides, TyG index, total and LDL cholesterols, and an increase of HDL cholesterol in rats reflecting its insulin-sensitizing effect. It also reduced liver weight (Table 3) and, ALAT and ASAT activities (Table 4) which were highly increased by dexamethasone injection, traducing its hepatoprotective activity. The ability of this plant extract to manage insulin resistance could be related to its composition in flavonoids and saponins. Their presence in *E. coccinea* was confirmed by the studies of Obinna et al. [20]. In fact, flavonoids possess the properties of stimulating glucose storage in liver and muscle tissues [27], while saponins have antidiabetic and hypocholesterolemic effects [28]. Practically all the results obtained revealed that the extract at dose of 215 mg/kg has presented the best insulin sensitizing effect; it was the therapeutic dose.

5. Conclusion

In conclusion, the results of this study indicates that aqueous extract of *E. coccinea* exhibited a α-amylase inhibitory activity and insulin sensitizing effect by reducing blood glucose level and improved dyslipidemia. Our findings therefore revealed that aqueous extract of *E. coccinea* possess a good potential for alleviating diabetes.

Data availability

We have the data of this research article and can provide it as per the request.

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Declaration of competing interest

The authors declare that they have no conflicts of interest.

CRediT authorship contribution statement

Sl Poualeu Kamani: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization. **J. Kamgaing Waguia:** Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing. **D. Miaffo:** Writing – original draft, Writing – review & editing. **Ml Nchouwet:** Writing – original draft, Writing – review & editing. **Cl Demeni Kadji:** Investigation. **M.T. Wego Kamgaing:** Investigation, Writing – original draft, Writing – review & editing. **Rc Douho Djimeli:** Formal analysis. **J. Mzoyem Ngnitedem:** Investigation. **A. Kamanyi:** Supervision. **Sl Wansi Ngnokam:** Resources, Supervision.

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