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Original Article

Anti-hyperglycemic and Anti-hyperlipidemic Effects of Extract from *Houttuynia cordata* Thumb. in Streptozotocin-Induced Diabetic Rats

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ABSTRACT

Aim: Various properties of *Houttuynia cordata* Thumb. has been reported. However, few studies on its pharmacological effects have been documented. To elucidate whether there are more pharmacological effects of this plant, this study was therefore, carried out to determine the anti-hyperglycemic and anti-hyperlipidemic effects of 80% ethanol extract of *H. cordata* (HCE). Their antioxidant activity and acute toxicity were also conducted. **Methods:** HCE at a dose of 250 mg/kg was oral given to Streptozotocin-induced diabetic rats daily for 8 weeks. DPPH assay and HCE at the doses of 1,000, 2,000 and 3,000 mg/kg were employed in antioxidant and acute toxicity studies. **Results:** HCE lowered FBG in the diabetic, but not in the normal treated rats. HCE did not affect the body weight of all rats, but recovered TP, Alb, Glob, BUN, CREA, UA, TB, AST, ALT, ALP, and reduced the elevated CHO, TG and LDL in the diabetic rats. HCE possessed relatively low antioxidant activity with IC_{50} of 115.98± 0.82 µg/mL compared to Vitamin C (42.54+1.37 µg/ml), but did not produce any symptoms of acute toxicity. **Conclusions:** The extract of *H. cordata* may have beneficial properties and is a new agent for diabetic treatment and improve renal and hepatic functions.

Key words: *Houttuynia cordata* Thumb, Anti-Hyperglycemic, Anti-Hyperlipidemic, Antioxidant, Acute Toxicity.

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INTRODUCTION

Diabetes mellitus is a metabolic disease resulting from defects in insulin secretion or insulin action or both.[1] This disease often associated with high blood glucose (hyperglycemia), increase levels of TC, TG, LDL-C (hyperlipidemia), but decrease levels of HDL-C. The hyperglycemia can increase the incidence of many complications in diabetic patients[2-4] while hyperlipidemia contributes the development of coronary heart diseases and atherosclerosis, which are the most common cause of mortality and morbidity.[5]

Plukao (*Houttuynia cordata* Thunb.), is a herbaceous perennial plant and native to many countries in South-East Asia including Thailand. Its green leaves and young root are used as vegetable while dry leaves are used to prepare drink. The whole plant has been used for lowering the blood sugar and the treatment of diabetes. Major chemical components found in *H. cordata* are essential oil, flavonoid and alkaloids component.[6] The essential oil possessing anti-inflammatory, anti-bacterial and antiviral activities[7,8] and also effect on improving fat metabolism, urinary albumin and insulin resistance of diabetes mellitus.[9,10] The flavonoid components revealed antineoplastic, antioxidant, antimutagenic and free radical scavenging capacity.[11-13] The alkaloid components demonstrated significant potent antiplatelet and cytotoxic activities.[14] Quercitrin extracted from the leaves and stems, isoquercitrin from the floral spikes and fruit spikes showed diuretic action.[15,16] Methanol root extract showed a potential antioxidant and anticancer properties.[17]

Various plants have been used for the treatment of diabetes. However, there are few scientific reports supporting the antidiabetic properties of *H. cordata*. The purpose of this study was therefore carried out to investigate the anti-hyperglycemic and anti-hyperlipidemic effects of the ethanolic extract from *H. cordata* in streptozotocin-induced diabetic rats. An antioxidant activity of the extract was also evaluated. To see whether the extract is safe for administration, acute toxicity of the extract was examined as well.

MATERIALS AND METHODS

Plant Materials

The plant used in this study was *H. cordata* Thumb., purchasing from the local market in Chiang-mai Province, Thailand. The plant was identified by a Botanist in the department of Biology, Faculty of Science, Mahasarakham University, Thailand and the voucher specimens were deposited in the same University.

Plant Extract

The whole plants were washed thoroughly with tap water and dried at 50°C in an hot air oven. The dried plants (100 g) were powdered and macerated with 80% ethanol (1,000 mL) for 7 days. The mixture was

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filtered using filter paper. The filtrate was evaporated by using a rotary evaporator (Heidolph Laborota 4000, Germany) and dried by using a freeze dryer (Christ Alpha 1-4, Germany). The obtained 80% ethanolic extract of *H. cordata* (HCE) was kept at 4°C until be used.

Animals

Animals used in this study were male albino Wistar rats weighing 250-300 g purchased from the National Laboratory Animal Centre, Mahidol University, Thailand. The rats were housed under the conditions of 25 + 2°C, 50 + 5 % RH with a 12 h D/L cycle and maintained with free access to water and instant food for rodent. The experimental protocol and performance of the rats were approved by the Institutional Ethical Committee for the Purpose of Use and Control, and a Supervision on Experiment in Animals, Mahasarakham University, Thailand (License No.0012/2558)

Induction of Diabetes

The rats were injected intra peritoneally with a single dose of 65 mg/kg b.w. streptozotocin (STZ; Sigma Chemicals, St. Louis, MO) dissolved in 20 mM citrate buffer pH 4.5. After the injection, they were provided with 2% sucrose solution for 48 h to alleviate the discomfort after initiating the hypoglycemic phase. The rats with FBG at or above 126 mg/dL were used as the diabetic rats.[18]

Study on anti-hyperglycemic and anti-hyperlipidemic effects

The rats were randomly divided into 4 groups with 6 rats in each: group I: normal rats treated with 5% tween 80 (normal control group), groups II: diabetic rats treated with 5% tween 80 (diabetic control group), group III: diabetic rats treated with HCE (250 mg/kg b.w.), and groups IV: normal rats treated with HCE (250 mg/kg b.w.). Prior to the commencement of the experiment, HCE was suspended in 5% tween 80. HCE and 5% tween 80 were oral given to the rats once a day for 8 weeks. The volume of administration was 10 mL/kg b.w.

Determination of Fasting Blood Glucose

The normal and STZ-induced diabetic rats were fasted overnight and sacrificed before the collection of the blood samples from the tail vein of the rats. FBG was measured using Glucometer (Accuchek Adventage II, Roche, Germany).

Determination of Blood Biochemistry and Lipid Profiles

The blood samples were centrifuged at 1500 g for 10 min to separate blood serum. The serum was assayed for biochemistry including total protein (TP), blood urea nitrogen (BUN), creatinine (CREA), uric acid (UA), albumin (Alb), globulin (Glob), total bilirubin (TB), serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), and alkaline phosphatase (ALP), and also lipid profiles including cholesterol (CHO), triglycerides (TG), high density lipoprotein (HDL) and low density lipoprotein (LDL) by using an automatic blood chemical analyzer (BT 2000 plus, Germany).

Antioxidant activity Study

The antioxidant activity of HCE and of a standard solution (vitamin C) were determined using 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging method.[19] A total of 750 µL of HCE and vitamin C was added to 750 µL of DPPH in methanol solution. After incubation at 37°C for 20 min, the absorbance of each solution was determined at 517 nm using UV–VIS spectrophotometer. Corresponding blank readings were also taken and percent inhibition was then calculated as follows:

$$\%\text{inhibition} = [(\text{Absorbance control} - \text{Absorbance of test sample}) / \text{Absorbance of control})] \times 100$$

where A_{blank} is the absorbance of the control reaction and A_{sample} is the absorbance of the test compound

The IC_{50} value, the concentration of HCE required for 50% scavenging of the DPPH free radical, was determined from the curve of percentage scavenging plotted against the concentration, was also calculated. Each determination was done in triplicate.

Acute Toxicity Study

The rats were weighed and divided randomly into 4 groups with 6 rats in each; group 1; rats received 0.5% tween 80 (control group), group 2, 3 and 4; rats received 1,000, 2,000 and 3,000 mg/kg HCE respectively. HCE was once administered to the rats orally. Symptoms of toxicity (seizures, vomiting, diarrhea, and nausea) and rat mortality were observed within 24 h and over a further period for 14 days. On day 14, the rats were fasted overnight, weighed and sacrificed by using a cervical dislocation technique. The blood sample was then collected from the rat hearts for a determination of blood biochemistry and hematological values.

Statistical Analysis

All data were expressed as mean ± standard error of mean (SEM). Statistical analysis was carried out using One-Way ANOVA followed by Duncan's New Multiple Range Test. The criterion for statistical significance was at a p-value < 0.05.

RESULTS

Anti-hyperglycemic and anti-hyperlipidemic effects

Fasting Blood Glucose Levels

At an initial stage, FBG of the diabetic controls was significantly ($p<0.05$) higher than that of the normal controls. At the end of the experiments, FBG in normal rats and normal HCE treated rats were not different. However, FBG was significantly ($p<0.05$) reduced in the diabetic HCE treated rats comparing to that in the diabetic controls (Table 1).

Body Weight

Figure 1, the initial body weight of normal controls, normal HCE treated rats, diabetic controls, and diabetic HCE treated rats were not different. However, at the end of experiments, the body weight of normal controls and normal HCE treated rats were significantly *($p<0.05$)* higher than those of the diabetic controls and diabetic HCE treated rats which was not different.

Blood Biochemistry

As well recognized, blood chemistry; TP, Alb, Glob, BUN, CREA and UA involve renal function, while TB, AST, ALT and ALP involve in hepatic function.[20] Table 1, TP, Alb, Glob and UA in normal controls, diabetic controls, normal HCE treated rats, and diabetic HCE treated rats were not different. BUN in the diabetic controls significantly ($p<0.05$) increased compared to that in normal controls. HCE significantly ($p<0.05$) reduced BUN in the diabetic treated rats compared to that in the diabetic controls. However, BUN in normal controls and normal rats treated with HCE was not different. CREA significantly *($p<0.05$)* decreased in the diabetic controls compared to that in normal controls. Interestingly, HCE significantly *($p<0.05$)* increased CREA in diabetic treated rats and closed to that in normal controls.

TB, AST, ALT and ALP in diabetic controls significantly *($p<0.05$)* increased compared to those in normal controls. HCE significantly *($p<0.05$)* decreased TB, AST, ALT and ALP in the diabetic HCE treated rats. Fortunately, TB, AST, ALT and ALP in normal HCE treated rats did not differ from those in normal controls.

Lipid Profiles

Table 1, CHO and TG in diabetic controls significantly ($p<0.05$) increased compared to those in normal controls. Interestingly, HCE significantly *($p<0.05$)* decreased CHO and TG in diabetic HCE treated rats. Fortunately, CHO and TG in normal HCE treated rats were not

different from normal controls. HDL in diabetic control rats significantly *($p<0.05$)* decreased compared to that in normal controls. HDL in normal control, diabetic controls, normal HCE treated rats and diabetic HCE treated rats were not different. In addition, the difference of LDL in normal controls, diabetic controls, normal HCE treated rats, and diabetic HCE treated rats was not found.

Antioxidant activity

The study on antioxidant activity using DPPH scavenging activity revealed that HCE possessed relatively low potent antioxidant activity with IC_{50} of 115.98± 10.82 µg/ml comparing to Vitamin C (42.54 + 1.37 µg/ml).

Acute toxicity study

Symtoms of acute toxicity and body weight

All the doses of HCE did not produce any symptoms of acute toxicity or mortality of the rats during 24 h and over a further period lasting 14 days. The initial body weight of all rats was not different. And also at the end of the experiment the final body weight of HCE treated rats did not differ from those in control rats. (Figure 2)

Blood biochemistry

The toxicity study revealed that all the doses of HCE did not produce the alteration of TB, TP, Alb, Glob, BS; BUN, CREA, UA, AST, ALT, and ALP enzymes in the HCE treated rats when compared to those in controls (Table 2).

Table 1 : Fasting blood glucose levels, Blood biochemistry and Lipid profile in normal and STZ-induced diabetic rats.

Parameters		Groups			
		normal controls	Diabetic controls	Normal rats + HCE	Diabetic rats + HCE
FBG	Initial	94.4±4.09^{a}	348.2±24.83^{b}	99.17±5.17^{a}	359.67±14.90^{b}
	Final	86.33±5.13^{a}	530.33±16.86^{c}	91.66±5.13^{a}	415.33±12.66^{b}
TP (g/dl)	-	7.00±0.40	6.33±0.25	6.83±0.40	6.66±0.50
Alb(g/dl)	-	3.86±0.05	3.78±0.10	3.86±0.50	3.7±0.5
Glob(g/dl)	-	2.93±0.25	2.60±0.20	2.66±0.35	3.03±0.41
BUN(mg/dl)	-	20.83±2.35^{a}	54.65±2.75^{c}	19.03±0.80^{a}	42.30±2.60^{b}
CREA(mg/dl)	-	0.75±0.05^{b}	0.53±0.05^{a}	0.76±0.05^{b}	0.70±0.17^{ab}
UA(mg/dl)	-	1.60±0.90	1.60±0.50	2.4±0.20	1.8±0.2
TB(mg/dl)	-	0.66±0.5^{a}	0.95±0.5^{b}	0.63±0.11^{a}	0.80±0.10^{ab}
AST(U/L)	-	68.00±2.64^{a}	254.66±7.50^{b}	74.00±5.00^{a}	75.66±3.059^{a}
ALT(U/L)	-	36.5±0.50^{a}	156.33±3.51^{c}	24.00±10.14^{a}	59.66±9.50^{b}
ALP(U/L)	-	113.33±6.11^{a}	828.33±7.63^{c}	126.00±8.717^{a}	296.00±13.52^{b}
CHO (mg/dl)	-	59.50±0.50^{a}	155.50±10.50^{c}	75.33±16.07^{a}	116.33±21.77^{b}
TG (mg/dl)	-	80.33±8.50^{a}	440.00±11.00^{c}	105.00±6.00^{a}	145.00±33.00^{b}
HDL (mg/dl)	-	39.10±4.15^{a}	28.50±3.5^{a}	51.46±4.66^{b}	32.06±9.27^{a}
LDL (mg/dl)	-	45.00±2.00	47±8.00	41.00±11.35	47.75±11.59

According to Duncan's multiple range test, values within the same column followed by different superscripts are significantly different atp<0.05. FBG = fasting blood glucose, TP = total serum protein; Alb = albumin; Glob = globulin; BUN = blood urea nitrogen; CREA = creatinine; UA= uric acid; TB= total bilirubin; AST = serum aspartate aminotransferase; ALT = serum alanine aminotransferase; ALP = alkaline phosphatase, CHO = cholesterol, TG = Triglycerides, HDL= High density lipoprotein, LDL = low density lipopotein

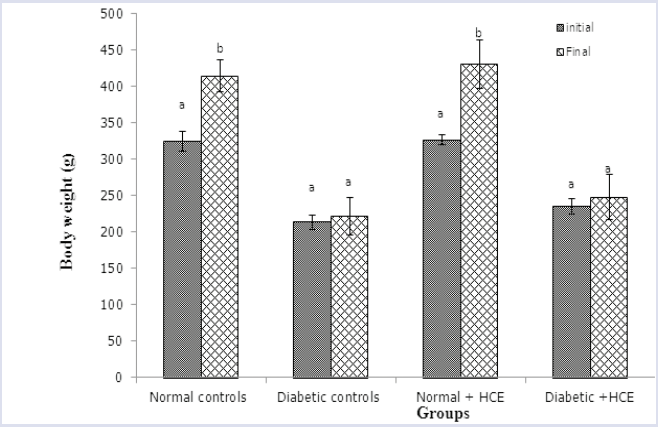

Figure 1 : Body weight in normal and STZ induced diabetic rats.

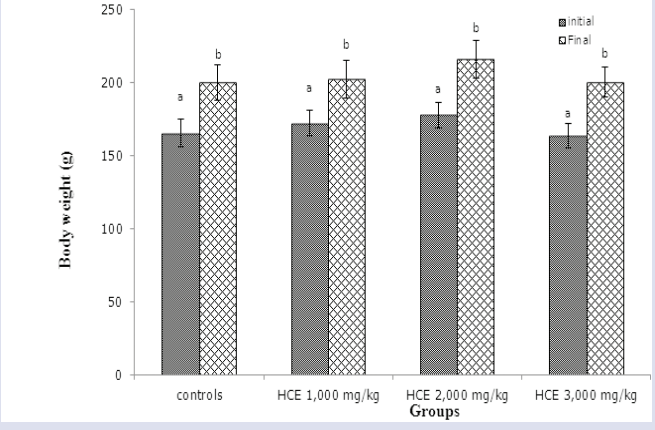

Figure 2 : Body weight of the rats treated with HCE 1,000, 2,000 and 3,000 mg/kg) and controls from acute toxicity study

Table 2 : Blood chemistry and Hematological values of the rats treated with HCE (1,000, 2,000 and 3,000 mg/kg) and control group from acute toxicity study

	Groups			
Parameters	Controls	HCE 1,000 mg/kg	HCE 2,000 mg/kg	HCE 3,000 mg/kg
TP (g/dl)	6.10±0.26	6.16±0.05	6.20±0.30	6.0±0.17
Alb(g/dl)	3.6±0.11	3.7±0.05	3.8±0.11	3.7±0.10
Glob(g/dl)	2.43±0.20	2.4±0.00	2.36±0.20	2.3±0.1
BUN(mg/dl)	19.26±1.59	19.90±0.9	19.70±2.20	19.83±1.35
CREA(mg/dl)	0.80±1.0	0.83±0.15	0.73±0.05	0.80±0.10
UA(mg/dl)	0.80±0.17	0.73±0.15	0.96±0.47	1.26±0.66
TB(mg/dl)	0.60±0.10	0.60±0.17	0.56±0.20	0.63±0.15
AST(U/L)	159.00±45.1	120.33±16.1	138.66±22.59	136.66±35.36
ALT(U/L)	36.33±11.01	30.66±4.61	43.66±3.21	36.33±4.5
ALP(U/L)	69.60±10.96	78.33±3.51	81.33±6.50	84.66±7.5
Hct (%)	48.00±3.60	48.66±1.15	49.33±1.52	49.66±2.08
Hb (%)	15.93±1.28	16.20±0.34	16.43±0.51	16.53±0.68
RBC ($\times 10^6/\mu L$)	8.50±0.56	8.24±0.35	8.55±0.30	8.5±0.52
WBC ($\times 10^3/\mu L$)	2.13±0.50	2.46±0.11	2.22±0.00	2.23±0.58

According to Duncan's multiple range test, values within the same column TP = total serum protein; Alb = albumin; Glob = globulin; BUN = blood urea nitrogen; CREA = creatinine; UA= uric acid; TB= total bilirubin; AST = serum aspartate aminotransferase; ALT = serum alanine aminotransferase; ALP = alkaline phosphatas, Hct = hematocrit, Hb = hemoglobin, RBC = red blood cells, WBC = white blood cell

Hematological values

Hematological values including Hct, Hb, RBC, and WBC in HCE treated rats were not different from those in control rats. (Table 2).

DISCUSSION

The present study was designed to investigate the anti-hyperglycemic and anti-hyperlipidemic effects of *Houttuynia cordata* Thumb, and to support its traditional use for the treatment of diabetes. In the present study, STZ (65 mg/kg bw.) was selected in order to destroy the pancreatic β-cells, and consequently, the STZ-injected rats become the diabetic rats.

HCE 250 mg/kg bw possessed a significant anti-hyperglycemic effect shown in the present study as it significantly reduced FBG in the diabetic treated rats. Unfortunately, HCE had no effect in normal rats, since FBG in the normal rats treated with HCE did not differ from that in normal controls. Previous study on *H. cordata* revealed the presence of essential oil in *H. cordata* and it has been shown to have an effect on insulin resistance of diabetes mellitus.[9,10] Flavonoids, alkaloids, saponin, tannin, and triterpinoids have been reported to possess hypoglycemic activity.[21] Therefore, the mechanism underlying the anti-hyperglycemic effect of this plant is partly due to the chemical compositions such as essential oil, alkaloids or flavonoids presence in *H. cordata*.

In the present study, the extract from *H. cordata* also showed the anti-hyperlipidemic effect as HCE significantly reduced CHO and TG which were increased in the diabetic control rats. In contrast, HCE slightly increased HDL which was reduced in diabetic control rats. β-myrcene, was frequently found in *H. cordata*[22] Lemongrass (*Cymbopogon flexuosus*) whose essential oil consists of equal amounts of myrcene and citral.[23] Lemongrass intake provides a beneficial effect of reducing the blood cholesterol level.[24] The underlying mechanism (s) on hypolipidemic effect of the extract from *H. cordata* may due to chemical constituent such as β-myrcene presence in *H. cordata*. HCE possesses an antioxidant activity but was less potent than Vitamin C. The antioxidant activity of HCE found in the present study is in line with the previous study which showed that the major chemical components found in *H. cordata* are essential oil, flavonoid and alkaloids component[6] The flavonoid components in *H. cordata* revealed antioxidant and free radical scavenging capacity.[11-13]

The obtained results of the anti-hyperglycemic and anti-hyperlipedemic effects of the extract from *H.cordata* in the present study are in accordance with the effects of various plant extracts and/or plant products such as the 80% ethanolic extract of *Pseuderanthemum palatiferum* at a dose of 250 mg/kg b.w administered daily and orally to the diabetic rats for 14 days showed hypoglycemic activity by significantly ($p<0.05$) decreasing levels of fasting plasma glucose (FPG) compared to that in normal controls,[25] the leaf extract from *Mimosa pudica* which showed high hypo-lipidemic activity by significant ($p<0.05$) decreasing serum cholesterol, triglyceride and LDL levels, but increasing HDL level when compared to those positive controls (standard drug),[26] the ethanol extract from the whole plant of *Mimosa pudica* which showed a significant hypo-lipidemic effect by decreasing the lipid profiles such as cholesterol, triglyceride and LDL levels but increasing in HDL level in the serum which was similar to the standard drug.[27] These results were also similar to the ethanolic extract of the aerial part of *Salvadora oleoides* Decne which produced a significant reduction ($p<0.001$) in blood glucose and also had beneficial effects ($P<0.001$) on the lipid profile in euglycemic as well as alloxan-induced diabetic rats, although the reduction in the blood glucose and improvement in lipid profile was less than that achieved with the standard drug tolbutamide.[28] The fresh leaf aqueous extract of *Clerodendrum capitatum* (CC) at the doses of 100, 400 and 800 mg/kg/day administering for 14 days significant ($p<0.05$, $p<0.001$) showed the dose dependent hypoglycemic and hypolipidemic effects in the treated rats.[29] And flower extract from *Sphagneticola trilobata* (L.) Pruski at the dose 250 mg/kg administering for 4 weeks significant ($p<0.05$) reduced the blood glucose levels, total cholesterol and low density lipoprotein in the diabetics but this is not in the normal rats. However, the extract had no effect on high density lipoprotein and triglyceride.[30] HCE showed any

symptoms of acute toxicity in the present study suggesting that it is safe for administration.

CONCLUSION

In conclusion, *H. cordata* can be used as traditional medicine for diabetic treatment. HCE at a dose of 250 mg/kg shows a beneficial anti-hyperglycemic and anti-hyper-lipidemic effects in diabetic rats. HCE also improves the renal and hepatic functions resulting from diabetic state. HCE at the dose up to 3,000 mg/kg, did not produce any signs or symptoms of an acute toxicity and mortality of the rats throughout the period of observation for 24 h and a further period lasting 14 days, indicating HCE has no acute toxicity. Consummation of *H. cordata* may be a good resource for reducing a risk of diabetes, coronary heart diseases (CHD) and/or atherosclerosis. For further studies, isolation and investigation of the chemical constituents of *H. cordata* responsible for the anti-hyperglycemic and anti-hyperlipidemic effects should be undertaken in order to elucidate the underlying mechanism(s) of these activities.

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CONFLICT OF INTEREST

No conflict of interest are declared.

ABBREVIATIONS USED

HCE : *Houttuynia cordata* Thumb. Extract**; FBG:** Fasting blood glucose**; mg :** milligram **; kg :** kilogram**; TP:** total serum protein**; Alb :** albumin**; Glob :** globulin**; BUN :** blood urea nitrogen**; CREA :** creatinine**; UA :** uric acid**; TB:** total bilirubin**; AST :** serum aspartate aminotransferase**; ALT :** serum alanine aminotransferase**; ALP :** alkaline phosphatase**; CHO :** cholesterol**; TG :** Triglycerides**; HDL :** High density lipoprotein**; LDL :** low density lipoprotein**; IC50** : Half maximal Inhibitory Concentration; **µg :** microgram**; mL :** milliliter; **LDL-C** : low-density lipoprotein cholesterol**; HDL-C** : High density lipoprotein cholesterol; **g :** gram**; RH :** Relative Humidity**; h :** hour; **D :** day**; L :** light**; STZ :** streptozotocin**; mM :** millimolar**; pH :** Potential of Hydrogen ion**; dL :** deciliter; **b.w** : body weight; **DPPH** : 1,1-diphenyl-2-picrylhydrazyl; **µL :** microliter

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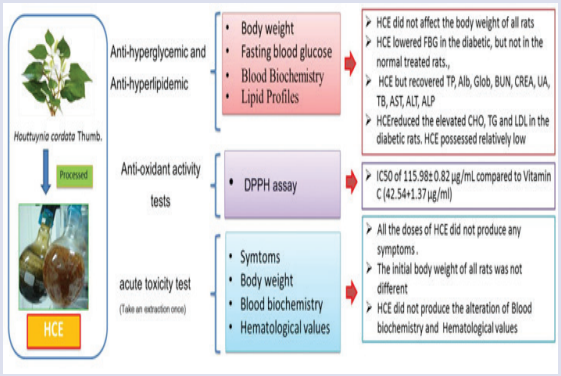
GRAPHICAL ABSTRACT



SUMMARY

- This paper is the first report about Anti-hyperglycemic and Anti-hyperlipidemic Effects of Extract from *Houttuynia cordata* Thumb. in Streptozotocin-Induced Diabetic Rats
- The extract prepared from dried *Houttuynia cordata* Thumb were powdered and macerated with 80 % ethanol for 7 days (HCE).
- Diabetic rats induction by streptozotocin (STZ; Sigma Chemicals, St. Louis, MO) a single dose of 65 mg/kg b.w.
- Anti-hyperglycemic and anti-hyperlipidemic was studied by repeat administration of HCE at the doses of 250 mg/kg for 8 weeks on Wistar rat models.
- Antioxidant activity was performed using free-radical scavenging activity (DPPH) assay.
- Acute toxicity was studied by repeat administration of HCE once administered to the rats orally at the doses 1,000, 2,000 and 3,000 mg/kg were observed within 24 h and over a further period for 14 days. on Wistar rat models.

AUTHOR PROFILE

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