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Research Paper

Evaluation of Extract Methanol *Brucea javanica* (EMoBJ) Seed on Blood Glucose Level in Diabetic Rats Induced-Alloxan

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ABSTRACT
Background *Brucea javanica (BJ) has become as important medicinal plant, which is used of traditional medicine healer to cure many diseases such as cancer, malarial and diabetics that has been increasingly the incidence of it.* ***The aim study. To*** *evaluated and compared the Hypoglycaemic and hypolipidaemic effects of extract methanol EMoBJ in alloxan-induced diabetic rats.* ***Methods*** *EMBJ and the standard drug glybenclamide and atorvastatin were orally administered daily to diabetic rats for 18 days. After the treatment period, blood glucose, glycosylated haemoglobin (HbA1C), Uric acid ;Total Cholesterol (TC) and and Triglyceride (TG), were determined.* ***Result*** *The levels, blood glucose, serum lipids;Total Cholesterol (TC), were significantly decrease ($p< 0.05$), however HbA1C, Uric Acid, TG were not significantly ($p < 0.05$) decreased in alloxan-induced diabetic rats. Compared with the normal control rats, significantly higher blood glucose levels were observed in the alloxan-induced diabetic rats Treatment of the diabetic rats with EMoBJ and glybenclamide restored the changes of the above parameters to their normal level after 18 days of treatment.* ***Conclusion*** *That EMoBJ had possessed hypoglycaemic and low to hypolipidaemic activities in alloxan-induced in diabetes mellitus (DM) rats model.*
KEYWORDS*: alloxan; diabetic; Brucea javanica; hypoglycaemic; hypolipidaemic; EMoBJ*

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I. INTRODUCTION

Diabetes in now day is common chronic diseases globally. It can cause morbidity and mortality in population marked by high blood glucose or hyperglycemia. It come from the impaired insulin secretion of pancreatic beta cells and cellular resistance to insulin.[1] Diabetes mellitus (DM) is metabolic diseases associated with endocrine and metabolic disorders, that characterized by hyperglycemia, with a genetic predisposition. DM leads to abnormal metabolism of carbohydrates, fats and proteins.[2] Depend on the circulating of glucose arises from endogenous liver production and exogenous food intake make the level of blood glucose any change. In other case, maintaining circulating glucose concentrations, glucose is needed, that can be derived by either breaking down glycogen stores in the liver or gluconeogenesis in the liver and kidney. High glucose in circulating, can stimulates pancreatic β-cells to secrete insulin and, in turn, the elevated insulin concentrations decrease glucose concentrations by stimulating peripheral tissue glucose uptake. The balancing of the glucose–insulin in system is the central point to the dynamics of maintaining glucose regulation in the body.[2]

According to the (WHO), more than 220 million people or 2.8% of the population worldwide suffer from diabetes.[3] Its incidence is increasing rapidly, and is estimated that by the year 2030, this number will almost 5,6 %, as a new problem global epidemic with the people around the world. DM affects human tissues in kidneys eyes, hearts, nerves and blood vessels. According to previous reports, diabetes mellitus has become the third most serious threat to human health following malignant tumors and cardiovascular and cerebrovascular disease.[4] The greatest increase in prevalence is expected become running on in Asia area and also in Africa. The incidence of diabetes in high in developing countries can be follows from the trend of urbanization and lifestyle changes. To manage the level of glucose seems the main goal in current to treatment of diabetes maintaining strict control of glycemia by using of drug oral hypoglycemic agent and insulin or combination of both.

Up to 90% of all diagnosed cases of diabetes are type 2 diabetes (T2D), a chronic and progressive metabolic disorder with uncontrolled glucose concentrations.[5,6] The involving of Insulin resistense (IR) that is a pathogenesis of T2D, in which most tissues do not use insulin properly. The ability of the IR to make the β-

cells secrete more insulin to compensate is needed. Thus, hyperinsulinemia is usually appear and can be observed in prediabetic patients. As long as β-cells can provide sufficient insulin, IR can last for decades without leading to disease. The occurrence of β-cells uncontrolled of hyperglycemia as do not function adequately to provide enough insulin, perhaps due to genetic factors. Thus, the two key elements in the pathology of T2D are IR and β-cell dysfunction.[7,8] In Current, available oral antihyperglycemic agents, even when used intensively, are often unable to control the hyperglycemia and the disease is not going well. Ideally oral treatment for diabetes would be a drug that not only controls the glucose level but also prevents the development of hyperlipidemia and other complications of diabetes. Unfortunately, among the currently available drugs, the choice of drugs is to have a side effects from mild, to moderate and severity in human eyes, kidneys, hearts, nerves and blood vessels. According to previous reports, diabetes mellitus has make become the third most serious threat to human health following malignant tumors and cardiovascular and cerebrovascular disease.[2,7.8]

Currently, herbal medicine has been a choice of used to cure of diabetic diseases. There was B javnica , it is used the seed as a herbal medicine. The seed of *Brucea javanica (B. javanica),* belonging a family of Simaroubaceae, is a shrub which is mostly originated in Sumatera and Java of Indonesia, Southeast Asia, and Northern Australia. The traditional folk medicine, of Indonesia used the seed of this plant has been used for the treatment of malaria, dysentry, diabetes and various disorders among indigenous peoples in Indonesia and others with the bitter principle tasted of quassinoids. The Chemical compounds have been reported that isolated from this plant including alkaloids, lignans and terpenoids, alkaloid glycosides, quassinoid glycosides, and quassinoides. The Quassinoids are known to be the major compounds from *Simaroubaceae* family and they possess a variety of biological activities such as anticancer, antitumor and antimalarial. It has been reported that quassinoid compounds bruceines derivatives, isolated from butanol fraction of B. javanica seed, that can reduce blood glucose concentration in short screening.[9.10,11] There is no report on EMBJ extract relating to antidiabetic and and antihyperlipidemic activity compared oral antidiabetic atorvaststitn. Atorvastatin (ATV) is a selective, competitive inhibitor of HMG-CoA reductase used in patients with diabetes and hypercholesterolemia and has been found to be safe and effective [2] In previous animal study atorvastatin inhibited increase in plasma glucose level and in clinical studies, patients with type II diabetes mellitus exhibited significant decrease. Based on these evidences the present study used as control agent. The aim of this study was, therefore, to evaluate the hypoglycemic properties the EMBJ of B. javanica seed through diabetics model in rat compared to control groups.

II. MATERIALS AND METHODS

2.1Chemicals

Alloxan monohydrate (Sigma Chemical Company), atorvastatin and glybenclamide (Indofarma Laboratories Ltd.,) were used in the study. All other chemicals were obtained from local sources and were of analytical grade.

2.2 Experimental Animals

SD male rats weighing 175–250 g were procured from the Local Laboratory Animal Resource Section, in Palembang Indonesia. The animals were housed in 30cm × 20cm × 15cm polivinyl chloride cages with 1 animal per cage and acclimatized for a period of 3 days. Individual animal was identified by a mark on cages were identified with label pasted on cages with relevant information. All animals were housed at a temperature of 25 ± 3°C and relative humidity of 30 to 70%. A 12:12 hr light: dark cycle was followed. All animals had free access to water and standard pelleted laboratory animal diet. The male animals were selected for the studies. The experimental protocol was approved by the Institutional Animal Ethics Committee. This study included 28 male rats induced diabetic by alloxan 30 mg/ 200gr ip. divide in 7 groups, 4 rats in each. The research protocol adhered to the "Principles of Laboratory Animal Care" Animals were received at 75 ±15 days of age.

2.3 Drugs Preparation and Administration

The ATV and Glibenclamide were suspended in vehicle (0.1% w/v suspension of Tween 80 and carboxymethylcellulose (CMC) in water). Animals were deprived of food for 1 hr before dosing. Glibenclamide(0,18 mg/kg) ATV(10 mg/kg) and EMBJ (50; 100 and 150 mg/200g) were administered in a single dose orally by gavage using a syringe fitted with suitable sized canula. Actual amount basically was decided on body weight. Volume of formulation administered was 0.5 ml per 200 g body weight.

2,4 Induction of Alloxan

Experimental diabetes was induced in rats by injecting alloxan monohydrate intraperitoneally at a dose of 30 mg/200g body weight. Alloxan was dissolved in Sodium Chloride 0.9% and injected immediately within few minutes to avoid degradation. After.Blood was collected from the tail of the rats and blood glucose levels were determined using glucometer test. Rats with blood sugar level of >200 mg/dl, as well as with polydipsia,

polyuria, and polyphagia were considered as diabetic and were employed in the study. Alloxan induced diabetic male rats SD were randomized into 7 groups of 4 rats each. (Normal rats, diabetic control, atorvastatin (ATV) 10 mg/kg. The rats were treated for 18 days and blood samples were collected at the end of therapy to assess HbA1c. These samples were analyzed for glucose level by glucometer. Changes in body weight, water, food intakes uric acid, TC and TG were also recorded. To evaluate the antihyperglycemic activity of atorvastatin and glibenclamide in alloxan-induced diabetic rats

2.5 Experimental Design

The rats were randomly divided into seven groups consisting of four rats each. Group 1 (normal control) consisted of normal rats that neither received alloxan monohydrate nor any drug. Group 2 served as positive control (diabetic control). Rats in Group 3 were diabetic and treated with EMoBJ (50 mg/200g;). Rats in Group 4 were diabetic and treated with EMoBJ (100 mg/200g;). Rats in Group 5 were diabetic and treated with EMoBJ (150 mg/200g;). Rats in Group 6 were diabetic and treated with atorvastatin (0.036 mg/200g;p.o.), where as diabetic rats in group 7 treated with Glibenclamide (1.8 mg/200g;p.o.). The drugs were given once daily for 18 days. The rats treated blood samples were collected at the end of therapy. These samples were analyzed for glucose level by glucometer. Changes in body weight, water, food intakes uric acid, TC and TG were also recorded. To evaluate the antihyperglycemic activity of atorvastatin and glibenclamide in alloxan-induced diabetic rats. Ethics for animal study research has been conducted by Local assesment No. 12/10/EASS/2016.

2.6 Estimate of Glucose Level

Blood samples were collected in 18 days of therapy, fasted rats at 1 hr after the last dose administration from the tail and analyzed for glucose by glucometer test. In addition, the changes in body weight, content were recorded in both the control and treated groups.

Blood HbA1c, and TG Blood HbA1c was measured by spectrofotometic test meters (Metrika, Sunnyvale, CA). after 18 days of Treatment . Using Laboraroty of Health Palembang During September – December 2016.

Blood glucose Level; Uric Acid and TC Blood glucose was measured at the time from the tail, using glucometer test (Gluco DR) ®.

Plant Material. The plant materials were purchased from the Yogyakata Herbalstore, Indonesia, The plants were identified at the School of Pharmacy in Yogyakarta Research. The names of these medicinal plants, their families, local name, parts used, and voucher specimen numbers for the experiments are *Brucea javanica.*

2.7 Plant Extracted Preparation.

The dried and ground seed of *B. javanica* (2 kg) were macerated twice in 5 L of methanol (MeOH) for 5 days min. The methanol solution was then filtered. The solvent was removed in vacuo by evaporator apparatus rotary to have recidual (Crude extract) During September December 2016.

HNMR and CNMR Assay of EMBJ Spectroscopy was treated to have HNMR and CNMR data in CdCl3 solvent; FTIR in Spectrosscopy(JOEL Appartus). These data has been obtained previously.

2.8 Statistical Analyses

The results were expressed as mean ± SD. All the data were analyzed t-test and Anova followed by Dunnett's.. A value of $P < 0.05$ was considered as statistically significant.

III. RESULT AND DISCUSSION

The effects of the differently doses of EMoBJ on the fasting blood glucose levels by alloxan-induced diabetic rats are shown in Table 1. The administration of a single intraperitoneal injection of 30 mg/200gr body weight of alloxan monohydrate induced diabetes in rats after 72 h. The fasting blood glucose levels in alloxan-induced diabetic rats were 263±14,3 - 442±30.3 mg/dL . The fasting blood glucose levels of the diabetic model rats were significantly higher than that of the normal control group.

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TABEL 1 Effect of EMoBJ on, blood glucose, TG, TC Uric acid , and glycosylated haemoglobin

	1	2	3	4	5	6
GROUP	BodyWeight BW (Grm)	Glucose mg/dL	Uric Acid mg/dL	TG Mg/dL	HbA1c (%)	TC Mg/dL
Normal Control	225± 21.5	78 ±17,2	3.1±0,2	115±4,7	4,02±0,5	171,5±26,1
Diabetic Control	207± 18.0	442±30.3	7,7±3,3	146±73,2	4,07±0,9	75,5±17,8

EMoBJ (50 mg)	210± 22.3	344±50.3	9,1±6,3	137,6±21,6	4,57±1,0	65,2±17,8
EMoBJ (100 mg)	206± 19.5	360±33.2	9,7±3,9	119,5±9,4	4,47±0,75	72,5±24,5
EMoBJ (150 mg)	192± 15.0	385±36.8	2,9±0,5	114,2±50,7	4,56±0,90	124,6±36,4
Diabetic (Atorvastatine)	207± 25.0	310±8.0	4,7±0,6	129±52,8	4,55±0,98	132,5±27,4
Diabetic (Glibenclamide)	189± 14.0	263 ±14,3	6,9±5,0	147,0±36,5	4,52±0,90	106,0±61,7

Type I diabetes is an autoimmune disease. This disease, needs insulin injections to survive, which sometimes cause a series of complications. To pursuit and the development of safer, more specific and more effective of hypoglycemic agents are becoming important. Therefore, this study is the preliminary assessment and comparison of the anti-diabetic activities of differently doses of EMoBJs. The diabetic model was developed by the intraperitoneal injection of alloxan.[12]

Chemically, alloxan is a hydrophilic agent that chemical is unstable of pyrimidine derivative. Alloxan is one of the common substances administered to induce diabetes mellitus model in rats. Alloxan much have antiradicals, has a destructive effect on the pancreatic β cells due to can generate a massive amount of oxygen radicals .[12] As long to the literature survey, alloxan monohydrate is known work as selective pancreatic islet beta cell cytotoxicity effect and has been extensively used to induce diabetes mellitus in animals model. The mechanism of diabetic desease to develop due to its pathogenesis and progression of diabetic involved in oxidative stress that has been suggested in developing diseases including cardiovascular diseases, chronic kidney disease, ageing, and diabetes. Studies have shown that free radicals can rapidly accumulate and lead to oxidative stress in diabetic animals, which might impair the function of the liver and kidney, followed decrease antioxidase activities and increase lipid peroxidation levels. Therefore, the role of oxidative stress/antioxidant to balance diabetes and its complications is an important and interesting research topic. Much attention has been focused on the research of antioxidant substances.[13] [14]

In general, oxidative stress work by broken the molecular compound in cells to develop diseases.[12,13] ·The herbalist evidence has proven that the use of herbal medicine is a viable alternative for the control of diabetes and other diseases. Herbal medicine has chosen as alternative agent to cure the chronic diseases, [15,16] due to the beneficial properties of herbal medicine include significant efficiency, fewer side effects, relative safety, and also especially low cost for a patient who cannot afford precious medication.[17,18] In fact, the medicinal plants are important natural sources of molecules with potential antidiabetic effects. Many plant species have been reported to have hypoglycemic effect, which may act through different mechanisms, including inhibition of alfa glucosidase, inhibition of DPP-IV, inhibition of glycogen phosphorylase and/or enhancement of insulin secretion, and newer SGLT-2 inhibitor. Not only stimulation of glucose uptake but also to let the carbohydrate intake to let him loose in to the intestine.[19] The scientists has led to make great efforts by the wide diversity of plant species to pursuit bio prospect plants that may contribute to the control of diabetes.[20]

In this study the methanol extract of *B. javanica* seed (EMBJ) was done and tested for antidiabetic activity using alloxan-induced in diabetic rats. Further evaluation of hypoglycemic effect on indicated that rats treated with (50 mg/kg bw) showed a 39.91% decrease ($P < 0.05$) in blood glucose levels at , and continuous fall ($P < 0.05$) of 28.89% and 20.29% was observed in the following 18 day compared to the normal control was lost (4.6-fold) after removal. These results concluded that the EMoBJ inhibitory activity initially detected was primarily due to the compounds named quassinoids.[14] Change in initial and final of body weight (BW) of normal control and experimental groups are shown in the data. Marked of BW loss was observed in diabetic rats.[3,5,10] The data obtained from this study showed that the treatment of EMBJ and glibenclamide may protects the diabetic rats from massive BW loss, when given orally, daily for eighteen days. EMoBJ - and glibenclamide-treated rats showed to recovery the final BW of rats which is near to that of normal control rats. Moreever, the weight gain was lesser in the diabetic rats when compared the group of treatment versus normal control rats. Thus, the BW loss can be due to catabolic effects that seen in diabetic rats was only partially attenuated by the seed extracts of EMoBJ.[11,12,13]

Atorvastatin and Glibenclamide alone and in combination showed significant fall in blood glucose level compare to baseline. Fall in glucose level was significantly more in low dose individually and also improved the body weight loss[14,15]. The weight gain was significantly more in doses treated rats as compared to

positive control group and greater than those who received atorvastatin and gliblenclamide alone. Rats treated also reported significant decrease in blood uric acid level. Fit to the Burcea has a antidiabetic activity.

IV. CONCLUSION:

Increasing of hypoglycemic effect and decreasing of uric acid level may be due to potentiation or synergism of total quassinoid in EMoBJ. Further studies are required to demonstrate clinically significant antidiabetic effect and to low uric acid.

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