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EFEK EKSTRAK DAUN SIRSAK (*amona muricata*) TERHADAP PENURUNAN KADAR TRIGLISERIDA PADA MODEL TIKUS DIABETES MELITUS

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ABSTRAK

Diabetes melitus merupakan sindrom metabolik dengan karakteristik hiperglikemia kronis, akibat kurangnya produksi insulin, atau penurunan sensitivitas terhadap insulin atau gabungan keduanya. Hal ini menyebabkan gangguan metabolisme karbohidrat, lemak, dan protein. Terapi dengan menggunakan obat sintetis memerlukan biaya yang tidak sedikit dan menimbulkan efek samping hal inilah yang mendorong masyarakat mulai beralih menggunakan pengobatan tradisional. Sirsak merupakan buah yang banyak dibudidayakan yang daunnya memiliki kandungan flavonoid tinggi yang dapat berperan sebagai antioksidan untuk memperbaiki metabolisme pada penderita diabetes mellitus. Penelitian ini bertujuan untuk mengkaji efek dari daun sirsak (*amona muricata*) terhadap penurunan kadar trigliserida dan mengetahui dosis efektif ekstrak daun sirsak dalam menurunkan kadar trigliserida. Jenis penelitian eksperimental laboratories pre test and post test with control group design, jumlah sampel 30 ekor tikus. Tikus diinduksi menggunakan aloksan, dan kadar trigliserida ditentukan dengan metode spektrofotometri. Ekstrak daun sirsak memiliki kemampuan dalam menurunkan kadar trigliserida. Penurunan kadar trigliserida ditunjukkan pada kelompok ekstrak 800 mg sebesar 38,23 % dan kelompok 400 mg sebesar 23,66 %.

Kata kunci: Aloksan, Antihiperglikemi, Diabetes, Trigliserida dan Ekstrak Daun Sirsak

ABSTRACT

Diabetes mellitus is metabolic syndrome with the characteristics of chronic hyperglycemia. The cause of this conditions are the decrease of insulin level, insensitivity insulin of tissue or combination of both. Therapies using synthetic drugs required not a small cost and caused side effects which began to drive people to switch and use traditional medicine. This study aimed to assess the effect of Soursop leaves (*Annona muricata*) towards the decrease of triglyceride blood levels and determine the effective dose of soursop leaf extract as an anti-diabetic. The experimental research laboratories pre-test and post-test with control group design, sample amounts were 30 rats, using alloxan to induce diabetic, and triglyceride levels were determined by spectrophotometri technique method, data analysis using SPSS for windows. Soursop leaves extract has the effect to decrease triglyceride levels in diabetic rats induced which alloxan. Extract 800 mg group had the effect of decreasing triglyceride levels the most is 38.23% and then 400 mg group with 23.66%.

Keywords: Alloxan, Anti-hyperglycemia, Diabetic, Triglyceride level and Soursop leaves extract

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UJI AKTIVITAS ANTIOKSIDAN EKSTRAK ETANOL DAUN SIRSAK (*Annona muricata* L) PADA TIKUS PUTIH (*Rattus norvegicus*) DIABETES MELITUS YANG DIINDUKSI ALOKSAN DENGAN PARAMETER MALONDIALDEHID (MDA)

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ABSTRACT

Hyperglycemia in Diabetes can caused the excessive production of Reactive Oxygen Species (ROS) in the body that will causes oxidative stress that tissue damage. Oxidative stress can indicated by increasing MDA levels. This research aims to know and determine the concentration ethanol extract of soursop leaves that have antioxidant activity to MDA levels in diabetic rats. 9 white rats were divided into 3 groups. All rats were induced by alloxan 110mg/Kg.BB intraperitoneally. Group I was administered with Na.CMC as a negative control, group II and III were administered with ethanol extract of soursop leaves 2,5% and 5%. Administration were given orally for 12 days orally. Examination of blood glucose and MDA levels conducted before and after the administration. MDA Assay performed with TBA method was based on reaction of MDA-TBA as measured on a spectrophotometer 532 nm wavelength. The results were analyzed statistically by using randomized block design (RBD) method. Based on the research has been done, it was showed that the ethanol extract of soursop leaves can lower blood glucose levels of diabetic rats and extract with concentration of 5% has potential as an antioxidant activity that can reduce MDA levels in diabetic rat.

Key Words : Diabetes, Antioxidant, Malondialdehyde(MDA), Soursop Leaves

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THE EFFECTIVENESS TEST OF ETHANOL EXTRACT OF SOURSOP LEAVES (*Annona muricata* L.) TO LOWER BLOOD SUGAR LEVELS IN MALE WHITE RATS (*Rattus norvegicus*) INDUCED BY ALLOXAN

UJI EFEKTIVITAS EKSTRAK ETANOL DAUN SIRSAK (*Annona muricata* L.) UNTUK MENURUNKAN KADAR GULA DARAH TIKUS PUTIH JANTAN (*Rattus norvegicus*) YANG DIINDUKSI ALOKSAN

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ABSTRACT

Soursop leaves (*Annona muricata* L.) contain flavonoid compounds. Flavonoid compounds function as antidiabetic. The purpose of this study was to determine the effect of soursop leaf extract in reducing blood sugar levels in male white rats induced by alloxan. This study used 4 treatment groups, negative control was not given treatment, positive control was treated with 9 mg metformin, treated with the first dose of 7.2 mg and the last group was treated with the second dose of 14.4 mg. Before being given the treatment, the rats were fasted first and then checked for blood sugar, then the rats were induced by alloxan intraperitoneally (ip) then observed the development of the increase in blood sugar in the rats for 3 days and checked blood sugar levels once a day for 5 days. After that, it was continued with giving soursop leaf ethanol extract every day for 5 days. The results showed that soursop leaf extract can reduce blood sugar levels seen on days H4-H8 with a decrease of 6.67 mg/dl, for the treatment group sample 1 and 5.66 mg/dl, for the treatment sample 2. The test results using the Kruskal test -Wallis at 0.05 level showed that there was no significant difference using soursop leaf ethanol extract and metformin in lowering blood sugar levels.

Keywords: Soursop leaves (*Annona muricata* L.), Male White Rat, Flavonoids, Blood Glucose, Alloxan

ABSTRAK

Daun Sirsak (*Annona muricata* L.) mempunyai kandungan senyawa flavonoid. Senyawa flavonoid berfungsi sebagai antidiabetes. Tujuan dari penelitian ini untuk mengetahui pengaruh ekstrak daun sirsak dalam penurunan kadar gula darah pada tikus putih jantan yang diinduksi oleh aloksan. Penelitian ini menggunakan 4 kelompok perlakuan yaitu kontrol negatif tidak diberikan perlakuan, kontrol positif diberikan perlakuan dengan metformin 9 mg, perlakuan dengan dosis pertama 7.2 mg dan kelompok terakhir perlakuan dengan dosis kedua 14.4 mg. Tikus dipuasakan terlebih dahulu sebelum diberikan perlakuan, kemudian diperiksa gula darah, selanjutnya tikus diinduksi aloksan secara intraperitoneal (ip) kemudian dilihat perkembangan kenaikan gula darah pada tikus selama 3 hari dan dilakukan pemeriksaan kadar gula darah sehari sekali selama 5 hari, kemudian diberikan ekstrak etanol daun sirsak setiap hari selama 5 hari. Hasil penelitian menunjukkan bahwa ekstrak daun sirsak dapat menurunkan kadar gula darah dilihat pada hari H4-H8 dengan penurunan sebesar 6,67 mg/dl untuk kelompok perlakuan sampel 1 dan 5,66 mg/dl untuk perlakuan sampel 2. Hasil uji menggunakan uji Kruskal-Wallis pada taraf 0,05 menunjukkan bahwa tidak terdapat perbedaan yang signifikan menggunakan ekstrak etanol daun sirsak dan metformin dalam menurunkan kadar gula darah.

Kata kunci: Daun sirsak (*Annona muricata* L.), Tikus Putih Jantan, Flavonoid, Glukosa Darah, Aloksan

Uji Efek Pemberian Ekstrak Etanol Kulit Buah Sirsak (*Annona muricata* Linn.) Sebagai Antidiabetes Pada Tikus Putih (*Rattus norvegicus*) Yang Diinduksi Aloksan

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ABSTRAK

Tanaman yang digunakan dalam pengobatan herbal salah satunya adalah sirsak yang termasuk dalam famili Annonaceae. Annonaceae memiliki keanekaragaman kimia, sifat-sifat biologi dan farmakologi, seperti antimikroba, antifungal, sitotoksik, antitumor, dan insektisida dari alkaloid benzilisoquinolin, asetogenin, senyawa-senyawa C-benzilflavonoid, dan diterpenoid yang dihasilkan oleh tumbuhan ini.

Tujuan penelitian ini adalah untuk mengetahui efek ekstrak etanol kulit buah sirsak sebagai antidiabetes pada tikus putih yang diinduksi aloksan untuk membuat diabetes.

Penelitian yang digunakan adalah penelitian eksperimental laboratorium. Dengan menggunakan 15 ekor tikus yang dibagi dalam 5 perlakuan dengan 3 pengulangan.

Hasil penelitian menunjukkan bahwa kulit buah sirsak memiliki efek dalam menurunkan kadar glukosa darah pada dosis 50, 75 dan 150 karena dalam kulit buah sirsak terdapat senyawa-senyawa aktif yang berpotensi sebagai antidiabetes.

Kata kunci: ekstrak sirsak, antidiabetes, tikus putih

ABSTRACT

One of the plants used in herbal medicine is soursop which belongs to the Annonaceae family. Annonaceae has a variety of chemical, biological and pharmacological properties, such as antidiabetic, white rat antimicrobial, antifungal, cytotoxic, antitumor, and insecticide from benzylisoquinoline alkaloids, acetogenins, C-benzylflavonoid compounds, and diterpenoids produced by this plant.

The purpose of this research is to determine the effect of ethanol extract of soursop fruit peel as antidiabetic in alloxan-induced white rats on diabetes.

The research used is a laboratory experimental study, using 15 rats which were divided into 5 treatments with 3 repetitions.

The results showed that soursop fruit rind had an effect in lowering blood glucose levels at doses of 50, 75 and 150 because soursop fruit skin contained active compounds that have the potential as antidiabetic.

Keywords: soursop extract, antidiabetic, white rat

***Annona Muricata L* Leaf Infusion Effect on Glucose Absorption in the Intestinal Cells Membrane of Wistar Rats Model**

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Abstract

Background: Diabetes mellitus (DM) is a chronic disease that disrupts the homeostasis of glucose. DM is the second of most causes of deaths in urban areas, as well as the sixth in rural areas. Therefore, herbal medicine is constantly developed. Soursop leaves have been long known to have good effects in lowering glucose levels in our blood. This study explored the soursop leaves infusion on glucose absorption in the intestinal cell membrane of the *Wistar Rats* Model.

Methods: This was an exploratory study performed in October 2012 on five male rats *Wistar*, aged 3-4 months, weighing about 150-300 grams. Using the in situ perfusion method, each rat was given the following; 3 X 10⁻³ M glucose solution for one hour; 3 X 10⁻³ M glucose solution with 1 mL of infusion of soursop leaves (*Annona muricata L*) for one hour; 3 X 10⁻³ M glucose solution for the last hour. The glucose absorption levels were measured using spectrophotometry method. The glucose level between treatments was analyzed using a paired sample t-test.

Results: The concentration of glucose absorption was decreased, the first treatment was 24.42±14.29 mg/dL, the second treatment was 18.63±10.37 mg/dL, and the third treatment was 18.24±8.02mg/dL, however, the decrease of glucose absorption was statistically not significant.

Conclusions: There is a slightly decreased of the glucose absorption in the intestinal cell membranes of the *Wistar Rats* Model after infusion of soursop leaves. Further study is needed to explore the role of soursop leaves infusion in glucose absorption.

Keywords: Diabetes mellitus, glucose absorption, soursop leaves, *Wistar Rats*

**PENGARUH KOMBINASI EKSTRAK ETANOL DAUN SIRSAK DAN
GEMFIBROZIL TERHADAP KADAR TRIGLISERIDA DAN HDL TIKUS
YANG DIINDUKSI PAKAN TINGGI LEMAK**

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ABSTRACT

Soursop leaves ethanol extract (SLEE) has been shown to lower blood levels of total cholesterol. However, it not yet investigated the effects on triglyceride and HDL levels. There is also no research on combining related soursop leaves with gemfibrozil. The purpose of this study is to compare the efficacy of combination therapy SLEE and gemfibrozil to SLEE or gemfibrozil single treatment on decreasing triglyceride levels and increase HDL level in rats induced by high-fat feeding. Thirty male Wistar rats were divided into six groups (normal control, hyperlipidemia control, single gemfibrozil, single SLEE, 1st combination, and 2nd combination groups). Each group treated a high-fat feed two times a day for 14 days, except for the normal control. The test material was treated one time a day for five days. Measurement levels of triglycerides and HDL used GPO-PAP reagent and Direct Enzymatic Colorimetric Test. The data was analyzed by One-Way ANOVA test followed by Tukey's test. The results showed that SLEE can decrease triglyceride's level and increase HDL levels of male Wistar rats. The combination of SLEE and gemfibrozil also can decrease triglyceride's level and increase HDL level. However, there are no significances different between the efficacy of combination SLEE and gemfibrozil than SLEE or gemfibrozil single treatment in decreasing triglyceride's level and increase HDL levels of male Wistar rats.

Keywords: Hyperlipidemia, triglyceride, HDL, Soursop leaves ethanol extract, gemfibrozil.

UJI AKTIVITAS ANTIDIABETES EKSTRAK DAUN SIRSAK (*ANNONA MURICATA* L.) PADA MENCIT YANG DIINDUKSI ALOKSAN

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Abstrak

Diabetes mellitus masih menjadi salah satu penyakit dengan peringkat yang tinggi di Dunia. Penatalaksanaan diabetes yang masih cukup mahal dengan beberapa efek samping obat hipoglikemik oral, membuat tanaman herbal mulai menarik perhatian. Salah satu tanaman yang telah digunakan secara empiris sebagai antidiabetes adalah sirsak (*Annona muricata* L.) terutama bagian daun sirsak. Penelitian ini bertujuan untuk mengetahui efek dan dosis efektif ekstrak etanol daun sirsak terhadap penurunan kadar glukosa darah. Metode yang digunakan dalam penelitian ini adalah metode induksi aloksan. Hewan uji dibagi menjadi 5 kelompok, masing-masing kelompok terdiri dari 5 ekor. Kelompok I kontrol negatif CMC 0,5%, kelompok II kontrol positif glibenklamid, kelompok III ekstrak etanol daun sirsak 2,8 mg/20 g BB mencit, kelompok IV ekstrak etanol daun sirsak 4,2 mg/20 g BB mencit, kelompok V ekstrak etanol daun sirsak 5,6 mg/20 g BB mencit. Pemberian larutan uji dilakukan selama 14 hari setelah induksi aloksan dan pengukuran dilakukan pada hari ke-7 dan ke-14. Data yang diperoleh dianalisis dengan Kolmogorov-Smirnov dilanjutkan dengan anova satu arah dan uji *post hoc*. Hasil penelitian menunjukkan bahwa ekstrak etanol daun sirsak mengandung flavonoid, alkaloid, saponin dan tanin yang diduga memiliki aktivitas antidiabetes. Pada dosis 4,2 mg/20 g BB mencit merupakan dosis yang paling efektif dalam menurunkan kadar glukosa darah karena memiliki efek penurunan yang sebanding dengan glibenklamid.

Kata Kunci: Antidiabetes, aloksan, *Annona muricata*, glukosa darah, hiperglikemi.

Abstract

Diabetes mellitus is still one of the diseases with a high ranking in the world. Management of diabetes, which is still quite expensive with some side effects of oral hypoglycemic drugs, has made herbal plants start to attract attention. One of the plants that has been used empirically as an antidiabetic is soursop (*Annona muricata* L.), especially the soursop leaves. This study aims to determine the effect and effective dose of the ethanol extract of soursop leaves on reducing blood glucose levels. The method used in this research is the alloxan induction method. The tested animals were divided into 5 groups, each group consisting of 5 animals. Group I negative control CMC 0.5%, group II positive control glibenclamide, group III ethanol extract of soursop leaves 2.8 mg / 20 g weight mice, group IV soursop leaf ethanol extract 4.2 mg / 20 g weight mice, group V ethanol extract of soursop leaves 5.6 mg / 20 g weight mice. The test solution was given for 14 days after alloxan induction and measurements were carried out on the 7th and 14th day. The data obtained were analyzed by Kolmogorov Smirnov followed by one-way anova and post hoc test. The results showed that the ethanol extract of soursop leaves contained flavonoids, alkaloids, saponins and tannins which were thought to have antidiabetic activity. At a dose of 4.2 mg / 20 g weight mice is the most effective dose in reducing blood glucose levels because it has a lowering effect comparable to glibenclamide.

Keywords: Antidiabetic, alloxan, *Annona muricata* L., blood glucose, hyperglycemia.

**Efektivitas Kombinasi Ekstrak Etanol 96%
Daun Insulin (*Tithonia diversifolia*) dan Daun Sirsak (*Annona muricata*)
Sebagai Antihiperlipemik Pada Mencit Putih Jantan**

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ABSTRAK

Diabetes melitus (DM) merupakan suatu sindrom klinik yang ditandai dengan poliuri, polidipsi, dan polifagi, disertai peningkatan kadar glukosa darah atau hiperglikemia (glukosa puasa ≥ 126 mg/dL atau postprandial ≥ 200 mg/dL atau glukosa sewaktu ≥ 200 mg/dL). Indonesia diperkirakan pada tahun 2030 akan memiliki penderita DM sebanyak 21,3 juta jiwa. Obat yang digunakan untuk masyarakat penderita DM saat ini adalah Metformin terbukti memiliki efek samping yaitu flatulensi, mual, diare dan nyeri perut. Penelitian ini bertujuan untuk menguji efektivitas dan menetapkan dosis efektif kombinasi ekstrak etanol 96% daun insulin dan daun sirsak sebagai antihiperlipemik pada mencit putih jantan yang diinduksi larutan glukosa. Metode penelitian menggunakan 8 kelompok perlakuan dengan masing masing 4 ulangan, yaitu kelompok kontrol positif metformin (1,3 mg/20 g BB), kontrol negatif (akuades), kontrol normal (pakan), Dosis 1 (ekstrak daun sirsak 2,24 mg/20 g BB), Dosis 2 (ekstrak daun insulin 0,7 mg/20 g BB), Dosis 3 (daun insulin 0,7 mg/20 g BB dan sirsak 2,24 mg/20 g BB), Dosis 4 (daun insulin 0,7 mg/20 g BB dan 1,12 mg/20 g BB), Dosis 5 (daun insulin 0,35 mg/20 g BB dan 2,24 mg/20 g BB). Hasil penelitian menunjukkan bahwa dengan pemberian dosis kombinasi daun insulin 0,7 mg/20 g BB dan daun sirsak 2,24 mg/20 g BB terbukti efektif menurunkan kadar gula darah dengan rata rata 93,15 mg/dL. Berdasarkan hasil tersebut dapat disimpulkan bahwa dosis kombinasi daun insulin dan daun sirsak berpotensi menurunkan kadar gula darah.

Kata kunci : Antihiperlipemik; TTGO; Daun Sirsak; Daun Insulin

**Effectivity of 96% Ethanol Extract Of Insulin Leaves (*Tithonia diversifolia*) and
Soursop Leaves (*Annona muricata*) Combination as Antihyperglycemic
in White Mice**

ABSTRACT

Diabetes Mellitus is a clinic syndrome marked by polyuria, polyphagic, polydipsia accompanied by increasing of blood glucose levels or hyperglycemia (fasting glucose ≥ 126 mg/dL atau postprandial ≥ 200 mg/dL). It is estimated that by 2030, 21.3 million Indonesians will suffer from DM. The common drug used to treat DM patients, which proven to have side effects such as flatulence, nausea, diarrhea and abdominal pain. This study aim was to determine the effectivity of 96% ethanol extract of insulin leaves and soursop leaves

EFEKTIVITAS EKSTRAK DAUN SIRSAK (*Annona muricata*) TERHADAP KADAR MALONDIALDEHID HEPAR TIKUS DIABETIK SETELAH DIINDUKSI ALOKSAN

EFFECTIVENESS OF SOURSOP LEAF EXTRACT (*Annona muricata*) ON LIVER MALONDIALDEHYDE LEVELS IN ALLOXAN-INDUCED DIABETIC RATS

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ABSTRACT

Uncontrolled hyperglycemic triggers the formation of excess reactive oxygen species (ROS) in the body, causing fat peroxidation in cell membranes. The regulation of the amount of ROS can be measured through malondialdehyde levels. The purpose of this study was to determine the effectiveness of Soursop Leaf Extract (SLE) on levels of liver Malondialdehyde in diabetic rats. Thirty male Wistar white rats were grouped into (K1) standard feed and aquades, (K2) high-fat feed and vitamin E α -tokoferol 150 IU/kgBW/day, and groups using high-fat feed with three doses of SLE 75 mg/kgBW/day (K3), 150 mg/kgBW/day (K4), and 300 mg/kgBW/day (K5). Soursop leaf extract was given for 21 days after the 3rd day of alloxan induction and high-fat feed for 5 weeks. Data was analyzed with One Way ANOVA test and Post Hoc Least Significant Differences test. The results showed that in the K4 treatment group compared to the K3, K5 treatment groups and the K2 control group showed decrease in fasting blood sugar levels (131.1 mg/dL) and a decreased levels of Malondialdehyde (0.35796 nm/mL) which were better. The conclusion of this study is that soursop leaf extract effective to reduce Malondialdehyde levels with optimum dose 150 mg/kgBW/day.

Keywords: *Annona muricata*, diabetic, malondialdehyde

ABSTRAK

Hiperglikemik yang tidak terkontrol memicu pembentukan reactive oxygen species (ROS) yang berlebih di dalam tubuh sehingga menyebabkan peroksidasi lemak pada membran sel. Regulasi jumlah ROS dapat diukur melalui kadar malondialdehid. Tujuan penelitian ini untuk mengetahui efektivitas ekstrak daun sirsak (EDS) terhadap kadar Malondialdehid hepar tikus diabetik. Sebanyak 30 ekor tikus putih jantan galur Wistar dikelompokkan menjadi (K1) pakan standar dan aquades, (K2) pakan tinggi lemak dan vitamin E α -tokoferol 150 IU/kgBB/hari, dan kelompok yang menggunakan pakan tinggi lemak dengan tiga dosis EDS 75 mg/kgBB/hari (K3), 150 mg/kgBB/hari (K4), dan 300 mg/kgBB/hari (K5). Ekstrak daun sirsak diberikan selama 21 hari setelah hari ke-3 induksi aloksan dan pakan tinggi lemak selama 5 minggu. Analisis data menggunakan uji One Way ANOVA dan dilanjutkan dengan uji Post Hoc Least Significant Differences. Hasil penelitian menunjukkan bahwa pada kelompok perlakuan K4 dibandingkan kelompok perlakuan K3, K5 dan kelompok kontrol K2 menunjukkan penurunan kadar gula darah puasa (131,1 mg/dL) dan kadar Malondialdehid (0,35796 nm/mL) yang lebih baik. Kesimpulan penelitian ini bahwa ekstrak daun sirsak efektivitas menurunkan kadar Malondialdehid dengan dosis optimal 150 mg/kgBB/hari.

Kata Kunci: *Annona muricata*, diabetes, malondialdehid



Annona muricata Linn. leaf as a source of antioxidant compounds with *in vitro* antidiabetic and inhibitory potential against α -amylase, α -glucosidase, lipase, non-enzymatic glycation and lipid peroxidation



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Natural products

ABSTRACT

Annona muricata leaves are used in traditional medicine to manage diabetes mellitus and its complications. The aim of this study was to evaluate the potential *in vitro* antidiabetic properties of *Annona muricata* leaf by identifying its main phytochemical constituents and characterizing the phenolic-enriched fractions for their *in vitro* antioxidant capacity and inhibitory activities against glycoside and lipid hydrolases, advanced glycation end-product formation and lipid peroxidation. Ethanol extract of *A. muricata* leaf was subjected to a liquid-liquid partitioning and its fractions were used in enzymatic assays to evaluate their inhibitory potential against α -amylase, α -glucosidase and lipase, as well as their antioxidant (DPPH, ORAC, FRAP and Fe^{2+} -ascorbate-induced lipid peroxidation assays) and anti-glycation (BSA-fructose, BSA-methylglyoxal and arginine-methylglyoxal model) capacities. In addition, identification of the main bioactive compounds of *A. muricata* leaf by HPLC-ESI-MS/MS analysis was carried out. Ethyl acetate (EtOAc) and *n*-butanol (BuOH) fractions showed, respectively, antioxidant properties (ORAC 3964 ± 53 and $2707 \pm 519 \mu\text{mol trolox eq g}^{-1}$, FRAP 705 ± 35 and $289 \pm 18 \mu\text{mol trolox eq g}^{-1}$, and DPPH IC_{50} 4.3 ± 0.7 and $9.3 \pm 0.8 \mu\text{g mL}^{-1}$) and capacity to reduce liver lipid peroxidation ($p < .01$). Also, EtOAc and BuOH, respectively, inhibited glycation in BSA-fructose (IC_{50} 45.7 ± 13.5 and $61.9 \pm 18.2 \mu\text{g mL}^{-1}$), BSA-methylglyoxal (IC_{50} 166.1 ± 21.6 and $413.2 \pm 49.5 \mu\text{g mL}^{-1}$) and arginine-methylglyoxal (IC_{50} 437.9 ± 89.0 and $1191.0 \pm 199.0 \mu\text{g mL}^{-1}$) assays, α -amylase (IC_{50} 9.2 ± 2.3 and $6.1 \pm 1.6 \mu\text{g mL}^{-1}$), α -glucosidase (IC_{50} 413.1 ± 121.1 and $817.4 \pm 87.9 \mu\text{g mL}^{-1}$) and lipase (IC_{50} 74.2 ± 30.1 and $120.3 \pm 50.5 \mu\text{g mL}^{-1}$) and presented lower cytotoxicity, when compared to the other fractions and crude extract. Various biomolecules known as potent antioxidants were identified in these fractions, such as chlorogenic and caffeic acids, procyanidins B2 and C1, (epi)catechin, quercetin, quercetin-hexosides and kaempferol. This study presents new biological activities not yet described for *A. muricata*, which contributes to the understanding of the potential effectiveness in the use of the *A. muricata* leaf, especially its polyphenols-enriched fractions, for the management of diabetes mellitus and its complications.

**PEMBERIAN EKSTRAK DAUN SIRSAK (*Annona muricata*) UNTUK MEMPERBAIKI
KERUSAKAN SEL BETA PANKREAS MELALUI PENURUNAN KADAR GLUKOSA DARAH,
ADVANCED GLYCATION AND PRODUCT DAN 8-HIDROKSI-2-DIOKSISIGUANOSIN
PADA TIKUS WISTAR HIPERGLIKEMIA**

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ABSTRAK

Penelitian ini bertujuan untuk mengetahui efektifitas ekstrak daun sirsak untuk memperbaiki kerusakan sel beta pankreas pada tikus Wistar hiperglikemia yang diinduksi aloksan. Penelitian ini menggunakan rancangan *randomized posttest control only group design*. Penelitian ini menggunakan 24 ekor tikus Wistar yang dibagi menjadi empat kelompok, yaitu kelompok kontrol (K), dan tiga kelompok perlakuan (P). Kelompok P1 adalah kelompok perlakuan dosis ekstrak daun sirsak 50 mg/kg bb/hari. Semua kelompok diinduksi aloksan dengan dosis 150 mg/kg bb untuk memperoleh kondisi hiperglikemia.

Hasil penelitian menunjukkan terjadinya penurunan kadar glukosa darah setelah perlakuan, kadar glukosa pada kelompok K, P1, P2, dan P3 secara berurutan yaitu 208,0 mg/dL, 177,5 mg/dL, 164,7 mg/L dan 137,0 mg/dL. Setelah perlakuan 2 minggu terjadi juga penurunan kadar 8-OHdG dan kadar AGEs yang diamati, dimana kadar terendah terjadi pada perlakuan P3 dengan dosis 150 mgbb/kg berturut-turut 1,664ng/mL dan 0,033 mol/L, terjadinya perbaikan sel beta pankreas setelah pemberian ekstrak daun sirsak (*Annona muricata*) dengan dosis 150 mg/kg bb/hari. Berdasarkan hasil analisis GCMS, senyawa yang terdeteksi adalah kariofilen, etil tetradekanat, asam 2-sikloheksana-1-on, 4-hidroksi-3,5,6-trimetil-4-(3-oxo-1 butenil), etil heksa dekanat, fitol, Thiazol-2,4(3H, 5H)_dion, 5 benzilideno-3 [etifenilamino] metal], asam 9-oktadekanat, etil linoleat, etil oleat dan etil oktadekanat.

Kata kunci : Daun sirsak, Glukosa Darah, Hiperglikemia, AGEs, 8-OHdG

ABSTRACT

This research aimed to determine the effectivity of soursop leaf extract to repair beta pancreatic cells damaged in Wistar rats induced by aloxan. This experiment used *randomized posttest-only control group design*. In this experiment, 24 Wistar rats were used which divided into four groups, control group (K), and three treatment groups (P). P1 was the group treatment with a dose of 50 mg/kg bw/day, P2 with a dose of 100 mg/kg bw/day, and P3 was the group treatment with a dose of 150 mg/kg bw/day extract. All groups were induced by aloxan with a dose of 150 mg/kg bw to obtain condition of hyperglycemia.

The results showed that blood glucose levels decreased after treatment with the extracts. Glucose levels in group K, P1, P2, and P3 were 208.0 mg/dL, 177.5mg/dL, 164.7 mg/L and 137.0 mg/dL respectively. After 2 weeks of treatment, the level of 8-OHdG and AGEs were also reduced. The lowest level was observed in P3 treatment which the level of 8-OHdG 1.664ng/mL and 0.033 mol/L for AGEs level. In conclusion the soursop leaf (*Annona muricata*) extract given at a dose of 150 mg/kg bw/day can improve beta pancreatic cells resulted from antioxidant activity content in the extract which function as antihyperglycemia. Based on GC-MS spectra analysis, the the soursop leaf (*Annona muricata*) extract consisted of caryophyllene, ethyl tetradecanoate, acid 2-cyclohexane-1-one, 4-hydroxy-3,5,6-trimethyl-4-(3-oxo-1-butenyl), hexa ethyl decanoate, phytol, thiazole-2,4 (3H, 5H)_dion, 5 benzilideno-3 [etifenilamino] metal], 9-octadecanoic acid, ethyl linoleate, ethyl oleate and ethyl octadecanoic.

Keywords : Soursop leaf, blood glucose levels, hyperglycemia, AGEs, 8-OHdG

ORIGINAL CONTRIBUTION

Open Access

Possible anti-diabetic potentials of *Annona muricata* (soursop): inhibition of α -amylase and α -glucosidase activities



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Abstract

Background: *Annona muricata* has been used in folklore in the management of diabetes. A major strategy in decreasing postprandial hyperglycemia in diabetes involves the inhibition of carbohydrate-hydrolyzing enzymes - α -amylase and α -glucosidase. Thus, this study evaluated the in vivo and in vitro inhibitory potentials of the different parts (fruit-pulp, leaf, stem-bark and root-bark) of *Annona muricata*.

Methods: A total of 120 Wistar rats were treated with methanol extracts for 28 days after which blood and tissue samples were collected for α -amylase assay. In vitro inhibitory properties of methanol, ethyl acetate and dichloromethane extracts of the various parts of the plant on α -amylase and α -glucosidase activities were performed using standard procedures. The mode and mechanism of interactions between the enzymes and extracts (and isolated acetogenin) were determined using various kinetic interpolations and in silico experiments.

Result: The fruit-pulp and root-bark methanolic extracts better inhibited plasma and tissue amylase in vivo. The in vitro studies revealed that the stem-bark methanolic, fruit-pulp ethyl acetate, and leaf dichloromethane extracts better inhibited α -amylase activity compared with the standard acarbose. Also, the leaf methanol, fruit-pulp ethyl acetate, and root-bark dichloromethane extract better inhibited α -glucosidase activity. These observations were corroborated with their higher *B_{max}* and *V_{max}* and lower *K_d* values. All the extracts exhibited an "uncompetitive" type of inhibition pattern. Also, the isolated acetogenin (15-acetyl guanacone) from the fruit-pulp showed a better binding affinity compared to the standard drug, Metformin.

Conclusion: Better natural remedy for diabetics can be obtained from *Annona muricata* with minimal or no adverse side effects.

Keywords: *Annona muricata*, α -Amylase, α -Glucosidase, Acarbose, Metformin

Original Article

Effect of Graviola (*Annona Muricata* L.) and Ginger (*Zingiber Officinale Roscoe*) on Diabetes Mellitus Induced in Male Wistar Albino Rats

(diabetes mellitus / glucose transporters / insulin resistance / glycosylated haemoglobin / *Annona* / ginger)

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Abstract. *Annona* and ginger have prominent uses in traditional medicine; their therapeutic properties have not been sufficiently explored. The ameliorative effect of *Annona* or ginger extracts on hyperglycaemia associated with oxidative stress, inflammation, and apoptosis in experimentally induced diabetes was addressed. Type 1 diabetes in male rats was induced by a single injection of streptozotocin (STZ; 40 mg/kg, i.p.), then *Annona* (100 mg/kg) or ginger (200 mg/kg) extracts were orally administered daily for 30 days. The *Annona* and ginger extracts ameliorated hyperglycaemia, insulin level, glycosylated haemoglobin (HbA1c) and insulin resistance (HOMA-IR) levels in the diabetic rats. The treatments significantly ameliorated liver function enzymes and total proteins; this was confirmed by histopathological examination of liver sections. *Annona* and ginger extracts significantly reduced elevated malondialdehyde (MDA) and restored activity of antioxidant enzymes in the liver such as glutathione peroxidase (GPx),

glutathione reductase (GR), superoxide dismutase (SOD), and catalase (CAT) and the hepatic content of reduced glutathione (GSH). The oxidative stress-dependent inflammation was regulated by both *Annona* and ginger extracts, which was indicated by down-regulation of TNF- α , NF- κ B, pro-apoptotic proteins Bax, p53, and anti-apoptotic protein Bcl-2. Moreover, the expression of insulin receptor (*INSR*) and glucose transporter 2 (*GLUT2*) genes was markedly regulated by both these extracts. The results suggest that *Annona* and ginger extracts ameliorate the hepatic damage resulting from diabetes by advocating antioxidants and modulating apoptotic mediator proteins in the liver of diabetic rats. In conclusion, *Annona* and ginger extracts have a potential therapeutic effect in the treatment of diabetes and its complications.

Introduction

Diabetes mellitus (DM) is a metabolic disorder char-



Research paper

Antidiabetic and antioxidant effects of *Annona muricata* (Annonaceae), aqueous extract on streptozotocin-induced diabetic rats

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ABSTRACT

Ethnopharmacological relevance: The leaves of *Annona muricata* are used in Cameroon to manage diabetes and its complications. The aim of this study was to evaluate the antidiabetic, antioxidant activities and the potential toxicity of aqueous extract of *Annona muricata* in streptozotocin-induced diabetic rats.

Material and methods: Oral administration of *Annona muricata* aqueous extract (100 mg/kg or 200 mg/kg) was studied in normal and streptozotocin-induced diabetic rats. In long term treatment, 2 weeks after streptozotocin-induced diabetic rats, animals received plant extract during 28 consecutive days. For a protective effect, extract was administered 3 days prior to streptozotocin exposure and animals were observed 2 weeks without treatment.

Results: The plant extract was not effective in normal rats. In diabetic rats, single administration of the extract significantly reduced blood glucose levels by 75% and 58.22% respectively at the dose of 100 mg/kg and 200 mg/kg as compared to the initial value. Treatment of normal rats 3 days prior to diabetes induction showed that, *Annona muricata* extract has no effect within 72 h following STZ injection. However, after 14 days post-treatment, the extract at the dose of 100 mg/kg significantly reduced blood glucose levels as compared with initial value and diabetic control rats. Immunohistochemical staining of pancreatic β -cells of diabetic rats treated with the dose of 100 mg/kg expressed strong staining for β -cell compared to diabetic control. In a long-term study daily administration of *Annona muricata* aqueous extract for 28 days to diabetic rats, reduced blood glucose levels, serum creatinine, MDA, AST, ALT activity, and nitrite levels LDL-cholesterol. Total cholesterol, triglycerides, SOD, and CAT activity contents were restored.

Conclusion: These different results show that the antidiabetic activity of *Annona muricata* aqueous extract can be explained by its hypolipidemic effect, its antioxidant and protective action on pancreatic β -cells, which in turn improve glucose metabolism.

**THE EFFECTIVENESS OF SOURSOP/GRAVIOLA LEAF EXTRACT
(ANNONA MURICATA L.) ON THE LEVEL OF RAT PANCREATIC
MALONDIALDEHYDE (RATTUS NORVEGICUS) DIABETIC
HYPERCHOLESTEROLEMIA INDUCED BY ALLOXAN**

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ABSTRACT

Background: Hyperglycemia in diabetes mellitus causes oxidative stress which increases free radical production. The presence of higher malondialdehyde (MDA) level shows the increase of free radicals. Soursop leaf can act as an antidiabetic agent based on its role as antioxidant that binds free radicals and decreases MDA level. The aim of this research was to prove the effectiveness of soursop leaf extract (*Annona muricata* L.) on pancreatic malondialdehyde (MDA) level in alloxan-induced diabetic rats (*Rattus norvegicus*).

Subjects and Method: The subjects in this research were 30 rats and divided into five groups of treatment ie group I (Negative Control/KI), which was given distilled water and standard feed, group II (Positive Control/KII), which was given vitamin E 150 IU/kgBW/day, group III (KIII), which was given soursop leaf extract 75 mg/kgBW/day, group IV (KIV), which was given soursop leaf extract 150 mg/kgBW/day, and group V (KV), which was given soursop leaf extract 300 mg/kgBW/day. Each group consisted of 5 rats and was given soursop leaf extract for 21 days after being induced by alloxan and high-fat diet. Kruskal-Wallis test and Mann-Whitney test were used to process the data.

Results: Mann-whitney test showed significant difference in KI compared to KII, KIII, KIV, and KV due to their significance values being <0.05 ($p < 0.05$).

Conclusion: soursop leaf extract 150 mg/kgBW/day is the most effective dose on pancreatic MDA level reduction.

Keywords: Diabetes Mellitus, Soursop Leaf Extract (*Annona muricata* L.), MDA, Free Radicals

Antihyperglycemic effectiveness comparison of ethanol extract of soursop leaf (*Annona muricata* L.) againsts acarbose in streptozotocin-induced diabetic white rats

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Abstract. Type 2 diabetes mellitus is major health problem worldwide, including in Indonesia. Acarbose, an alpha glucosidase inhibitor, is one of oral pharmacologic management commonly used in clinical practice with potent side effect in long-term use. Flavonoid-and-tannins containing soursop leaf can stimulate insulin secretion and repair beta pancreatic cell dysfunction. This study was aimed to investigate the comparison on antihyperglycemic effect between ethanol extract of soursop leaf (*Annona muricata* L.) and acarbose in streptozotocin-induced diabetic white rats. This study was experimental research with pre- and post-test control group design enrolling 30 hyperglycemic white male rats. They were divided into 2 control groups (C(+)) was given by aquades and C(-) was given by acarbose) and 3 treatment groups (P1 was given 10 mg/200gBW extract, P2 was given 20 mg/200gBW extract, and P3 was given 30 mg/200gBW extract). Data analysis was using paired-T test. This study showed that there is a significant decrease in blood glucose levels in P1, P2, and P3 (95.08 mg/dL, 113.31 mg/dL, and 125.17 mg/dL; $p < 0.05$). Ethanol extract of soursop leaf has antihyperglycemic effect in dose-dependent response. The 30 mg of ethanol extract of soursop leaf is not inferior to 1.8 mg of acarbose in antihyperglycemic effect.

***In vitro* Antioxidant Properties and α -Glucosidase Inhibition of Combined Leaf Infusions from *Psidium guajava* L., *Syzygium polyanthum* L., and *Annona muricata* L.**

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ABSTRACT

Introduction: Guava (*P. guajava*), bay (*S. polyanthum*), and soursop (*A. muricata*) known as natural medicine. Limited report is available on their antioxidant and α -glucosidase inhibitory activities of leaf infusion. The aims of this research were to compare the antioxidant and α -glucosidase inhibitory activities of leaf infusion from guava, bay, and either as individual or combined infusions, and to analyze the chemical composition of the leaf infusion. **Methods:** Air dried leaf powder of guava, bay and soursop were infused separately with boiled aquadest. The infusions were analyzed for their antioxidant activity against DPPH. The α -glucosidase inhibitory assay was conducted against α -glucosidase from *Saccharomyces cerevisiae*. Then the infusions scanned with UV-Vis spectroscopy and analyzed with LC-MS. The synergism activities of the combined infusion were measured. **Results:** Antioxidant activities of leaf infusions of guava and bay showed a comparable result (IC_{50} 12.53 $\pm$ 0.55 and 10.76 $\pm$ 0.20 μ g GAE/mL, but the infusion of soursop showed lower (IC_{50} 19.77 $\pm$ 0.35 μ g GAE/mL) than BHT as positive control (11.6 $\pm$ 0.31 μ g GAE/mL). If soursop infusion was not added, then the mixture of the guava and bay infusion showed an antioxidative synergistic effect. The α -glucosidase inhibitory activities of the guava, bay and soursop infusion (0.083 $\pm$ 0.01; 0.025 $\pm$ 0.007; 0.533 $\pm$ 0.039 μ g GAE/mL, respectively) were stronger than acarbose (1285 $\pm$ 148 μ g/mL). The α -glucosidase inhibitory activities of the combined infusions showed a synergistic effect. The main constituents of the guava infusion were identified tentatively as chrysin and caffeoylquinic acid, for the bay infusion it was caffeoylquinic, and for the soursop infusion it was luteolin. **Conclusions:** There is a significant synergism of antioxidant activity of Guava and Bay mixture. The combined infusion of Bay and Soursop or Guava and Soursop showed antagonistic effect.

Key words: α -glucosidase, Leaf infusion, *Psidium guajava*, *Annona muricata*, *Syzygium polyanthum*, Synergism.