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Anti-Inflammatory, Anti-Apoptotic and Pro-Proliferative Effects of *Vitis Vinifera* Seed Ethanolic Extract in the Liver of Streptozotocin-Nicotinamide-Induced Diabetes in Male Rats

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Vitis vinifera seed ethanolic extract (VVSEE)

ABSTRACT

Objectives: Consumption of *Vitis vinifera* seed has been reported to ameliorate liver pathology in diabetes mellitus; however, the mechanisms underlying its effects remain unknown. In this study, the anti-inflammatory, anti-apoptotic and pro-proliferative effects of the ethanolic seed extract of *V. vinifera* (VVSEE) in the liver in cases of diabetes were identified.
Methods: Adult male rats with streptozotocin-nicotinamide-induced diabetes were given 50, 100 or 200 mg/kg body weight VVSEE orally for 28 days. At the end of the treatment, body weights were determined, and the blood was collected for analyses of fasting blood glucose, insulin and liver enzyme levels. Following sacrifice, livers were harvested and their wet weights and glycogen contents were measured. Histologic appearances of the livers were observed under light microscopy, and the expression and distribution of inflammatory, apoptosis and proliferative markers in the livers were identified by molecular biologic techniques.
Results: Treatment of rats with diabetes by VVSEE attenuates decreased body weight, liver weight and liver glycogen content. Additionally, increases in fasting blood glucose levels and liver enzyme levels and decreases in serum insulin levels were ameliorated. Lesser histopathologic changes were also observed: decreased inflammation and apoptosis, as indicated by decreased levels of inflammatory markers (TNF-α, NF-Kβ, IKK-β, IL-6, IL-1β) and apoptosis markers (caspase-3, caspase-9 and Bax). VVSEE treatment induces increase in hepatocyte regeneration, as indicated by increased PCNA and Ki-67 distribution in the livers of rats with diabetes. Several molecules identified in VVSEE via gas chromatography mass spectrometry might contribute to these effects.
Conclusions: The anti-inflammatory, anti-apoptotic and pro-proliferative effects of VVSEE could account for its hepatoprotective actions in diabetes.

Mots clés :
apoptose
diabète
inflammation
foie
régénération
extrait éthanolique de pépins de raisin de l'espèce *Vitis vinifera* (EÉPVV)

RÉSUMÉ

Objectifs : Il a été établi que la consommation de pépins de raisin de l'espèce *Vitis vinifera* améliore la pathologie du foie lors de diabète sucré. Toutefois, on ignore les mécanismes à l'origine de ses effets. Dans la présente étude, les effets anti-inflammatoires, anti-apoptotiques et pro-prolifératifs de l'extrait éthanolique des pépins de raisin de l'espèce *V. vinifera* (EÉPVV) sur le foie des personnes atteintes du diabète ont été établis.
Méthodes : Des rats mâles adultes ayant un diabète induit par injection de streptozotocine et de nicotinamide ont reçu 50, 100 ou 200 mg/kg de poids corporel d'EÉPVV par voie orale durant 28 jours. À la fin du traitement, le poids corporel des rats a été déterminé et leur sang prélevé pour mesurer la glycémie à jeun, les concentrations d'insuline et des enzymes hépatiques. Après avoir abattu les souris, leur foie a été prélevé pour en mesurer le poids et le contenu en glycogène. Les apparences histologiques des foies ont été observées sous microscopie optique, puis l'expression et la distribution des marqueurs d'inflammation, d'apoptose et de prolifération dans les foies ont été déterminées par des techniques de biologie moléculaire.

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Lampiran 2. (Jurnal 2)

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Hepatoprotective effects of hydroalcoholic extract of *Allium hirtifolium* (Persian shallot) in diabetic rats

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Abstract

Background: The prevalence of diabetes mellitus (DM) is dramatically increasing worldwide. Prospective studies have reported that high levels of hepatic enzymes, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), Alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) are associated with later development of diabetes. The aim of the present study was to examine the effect of hydroalcoholic extract of *Allium hirtifolium* (Persian shallot) on the level of liver enzymes in streptozotocin (STZ)-induced diabetic rats.
Methods: Thirty-two male rats were divided into four groups of eight. The diabetic groups received 100 and 300 mg/kg Persian shallot extract, the diabetic control and non-diabetic control groups received 0.9% saline for 30 days. At the end of the experimental period, fasting blood samples were collected, and enzymes levels were measured.
Results: Our findings showed that hydroalcoholic extract of Persian shallot can significantly decrease serum levels of liver enzymes (AST, ALT, ALP and LDH) in treated groups in a dose-dependent fashion ($p<0.05$).
Conclusions: Antioxidant micronutrients in the extract of Persian shallot may rehabilitate liver damages caused by free radicals in diabetic rats.

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Keywords: *Allium hirtifollium*; liver enzymes; Persian shallot; type 1 diabetes.

Introduction

Diabetes mellitus (DM) is characterized as a chronic metabolic disease featuring disturbances in carbohydrate, lipid and protein metabolism. DM is caused by either an inherited or acquired deficiency of insulin secretion and by decreased responsiveness of organs to insulin (1).

Investigators in this field believe that increased glucose levels can damage the liver and heart muscle cells, leading to an increase in alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyltransferase (GGT), alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) in blood (2). Aminotransferases are considered to be indicators of hepatocellular health; ALT and AST are found primarily in the liver. The liver plays important roles in the maintenance of normal glucose concentrations during fasting, as well as postprandially. It is also a major site of insulin clearance. The lack of a direct effect of insulin to suppress hepatic glucose production and glycogenolysis in the liver causes enhanced hepatic glucose production (3).

Previous investigations indicated that high levels of hepatic enzymes, including ALT and AST, are associated with later development of diabetes. Non-alcoholic fatty liver disease also accompanies elevation of ALT, which raises the possibility of a relationship between ALT and diabetes mellitus (4).

There is an increasing demand by patients for the use of natural products and other dietary modulators with anti-diabetic activity. This is due to the fact that insulin cannot currently be used orally, and repeated injections of insulin have many undesirable adverse effects. In addition, certain oral hypoglycemic agents are not effective for reduction of the blood glucose level in chronic diabetic patients (5).

It is widely believed that the antioxidant micronutrients obtained from fruits and vegetables afford significant protection against diseases. Onions are rich in two chemical groups that have perceived health benefits to humans. These are the flavonoids and the alk(en)yl cysteine sulphoxides (ACSOs). The ACSOs are the flavour precursors that, following cleavage by the enzyme alliinase, generate the characteristic odour and taste of onion (6). Flavonoids are potential antioxidants found in a wide variety of foods and onions. There are two major groups of flavonoids in onions, the flavonols and the anthocyanins, which have attracted interest in recent years. Intake of dietary flavonols and flavones has been reported to be inversely associated with the risk of cardiovascular disease in some epidemiological studies (7).

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Hepatoprotective effect of *Syringae vulgaris flos* ethanolic extracts in streptozotocin-induced diabetes in rats

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Abstract

Taking account of increasing world population life expectancy, health services will face with a large number of elderly people with chronic age-related diseases. It has been established that chronic diseases are usually accompanied by oxidative stress induced by the overproduction of reactive oxygen species damaging cellular constituents, under conditions of weakening antioxidant defense systems. The balance between free radicals and antioxidant endogenous systems has a defining role in preventing the damage of macromolecules. In addition to the enzymatic (catalase, superoxide dismutase, glutathione peroxidase, glutathione reductase) and non-enzymatic (vitamins A, C, E) endogenous systems, a good source of natural antioxidants are medicinal herbs products or phytochemical compounds. The aim of this study is to evaluate the hepatoprotective effect of *Syringae vulgaris flos* ethanolic extracts in a rat model of streptozotocin-induced diabetes.

Keywords: *Syringa vulgaris*, hepatoprotective effect, diabetes mellitus, streptozotocin.

Introduction

The increasing world population life expectancy, alongside the genetic predisposition and environmental factors such as excess food and lack of physical activity, will cause the augmentation of chronic age-related diseases.

Clinical and experimental studies revealed the major role that oxidative stress plays in the appearance or development of various pathological conditions. Oxidative stress, due mainly to an excessive production of reactive oxygen species (ROS) and impairing body antioxidant scavenger systems, is involved also in diabetes mellitus pathogenesis and its long-term complications (atherosclerosis, nephropathy, neuropathy or retinopathy). Based on body exposure to hyperglycemia, a consequence of insufficient insulin secretion or tissue resistance to it, diabetes is training complex metabolic changes, including hyperlipidemia, thus creating favorable conditions to the emergence of free radicals overproduction and advanced glycation end-products (AGE) formation and further damage of cells constituents [1, 2]. Many studies showed that the liver is affected in diabetes, which can increase the risk of nonalcoholic fatty liver disease (NAFLD) or hepatocellular carcinoma (HCC) appearance [3–5]. Therefore, therapeutic means must be found to prevent the excessive production of highly unstable ROS (superoxide anion radical, hydrogen peroxide), which is leading to damage of proteins, lipids, nucleotides or disulfide bonds altering cell membrane structure and disturbing its normal functionality [3–5]. Another strategy to prevent this cascade of events is improving either enzymatic (catalase, superoxide dismutase – SOD, glutathione peroxidase – GPx, glutathione reductase – GR) and non-enzymatic (vitamins A, C, E) antioxidant body defense systems. Thus, could be avoided oxidative damages of macromolecules which lead to necrosis and cell death or induce mutagenic conditions [1, 2, 6].

Researches were focused on finding natural antioxidants that improve tissues sensitivity to insulin action and also protect against damages caused by oxidative stress. It should be noted that there are numerous studies on plants and natural products thereof, which have the ability to lower blood sugar levels, improve lipid profile and prevent liver injury thereby maintaining body homeostasis [6–9]. Phytochemical constituents (flavonoids, polyphenolic acids, anthocyanins, tannins), which are found in all parts of the plant, could represent a natural source of antioxidants to support harmful free radicals scavenger or anti-glycation activities.

Syringa vulgaris (*Oleaceae*), worldwide known as lilac and recognized for its immunomodulatory virtues, is used as a traditional remedy in relieving pain cused by osteoarthropathy or gout arthritis [10, 11]. Studies regarding the beneficial role of verbascosides from *S. vulgaris* in experimental animal models of inflammation (colitis, spinal cord trauma, and periodontitis) [12–14] provide a scientific basis for its traditional use.

In this study, we aimed to identify polyphenolic compounds from two ethanolic extracts of *Syringae vulgaris flos* f. *álba* and f. *violácea* and assess their

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Olorunfemi R. Molehin* and Omotade I. Oloyede

Attenuation of oxidative stress and hepatic damage by white butterfly (*Clerodendrum volubile*) leaves in streptozotocin-induced diabetes in rats

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Abstract

Background: The negative impact of diabetes on the liver is well documented. The white butterfly (*Clerodendrum volubile*) leaf has been used in traditional practices for the treatment of various diseases, such as hypertension, diabetes, and rheumatism, but without scientific validation. This work was designed to evaluate the hepatoprotective properties of *Clerodendrum volubile* leaves on oxidative stress in streptozotocin (STZ)-induced diabetes in rats.

Methods: The rats were divided into ten groups of five rats each. Diabetes was induced by a single injection of STZ (65 mg/kg body weight; i.p), while the *C. volubile* extract (at the respective doses of 50, 100 and 200 mg/kg body weight) was given to diabetic and non-diabetic rats orally for 14 days. Metformin (100 mg/kg body weight) served as the positive control. Biochemical assays were conducted on the plasma for hematological parameters, along with hepatic marker damages and antioxidant enzyme determination *in vivo* to assess hepatic injury.

Results: The diabetic control rats showed significant increase ($p < 0.05$) in marker enzymes: aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and malondiadehyde with reduction in reduced glutathione, glutathione peroxidase, superoxide dismutase, catalase activities and plasma total protein content. Likewise, there were alterations in hematological indices in the diabetic control rats when compared with the normal control. However, treatment with *C. volubile* caused a reversal of the above parameters towards normal levels, thereby suggesting the modulating effect of the extract on oxidative stress, which may be a result of the high polyphenolic content and antioxidant capacity.

Conclusions: The protection of the liver tissues and the modulation of oxidative stress in STZ diabetic rats compare favorably to metformin, a standard antidiabetic drug.

Keywords: antioxidan; *Clerodendrum volubile*; diabetes mellitus; hepatotoxicity; histopathology; oxidative stress.

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Introduction

The liver is involved in a central and significant function in carbohydrate metabolism regulation. Its normal functioning roles maintains the blood glucose levels and the continuous supply of glucose to meet the organs needs in the body [1]. The liver is also involved in the detoxification of toxic substances and the synthesis of useful ones. Thus, any damage to the liver caused by hepatotoxic agents is of severe consequences to the body because its central metabolic role is impaired [2]. A significant portion of damage to the liver is induced by hepatotoxic chemicals through the means of lipid peroxidation and other oxidative damages [3, 4]. Furthermore, it is documented that liver injury resulting from a variety of damaging agents can induce necrosis, inflammation, fibrosis, cirrhosis and deterioration in the functional abilities of the liver [5, 6].

Diabetes is a disease condition affecting a large number of populations in the world [7, 8]. Several structural and functional liver abnormalities, which cause a derangement in the metabolism of carbohydrates, proteins and lipid, have been implicated in diabetes [9–11]. Growing evidence suggests that oxidative stress is a major culprit in the pathogenesis and progression of tissue damage in diabetes, which results in excessive glycogen deposition, cirrhosis and biliary disease in the liver of about 55%–80% of reported diabetic cases [3, 12, 13].

The treatment of liver disorders with the use of plants in folklore medicine is of immense pharmacological importance, because they could be potential lead sources for alternative therapeutic agents in hepatic injury prevention and management. Several plants with robust

Lampiran 5. (Jurnal 5)

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Anti-hyperglycemic and liver protective effects of flavonoids from *Psidium guajava* L. (guava) leaf in diabetic mice

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Keywords:
Psidium guajava L. leaf
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ABSTRACT

Guava leaf flavonoids were obtained using a simple extraction method to evaluate their anti-hyperglycemic and liver protective effects with a high-fat diet and a low-dose streptozotocin induced diabetic mouse model. Flavonoids supplementation significantly decreased fasting plasma glucose, glucose tolerance, and the insulin resistance index in diabetic mice, lowered the serum total cholesterol, triacylglycerol, and low-density lipoprotein cholesterol compared to the diabetic control group ($p < 0.05$). Furthermore, guava leaf flavonoids significantly decreased the liver and kidney indexes, and improved hepatocyte morphology in diabetic mice. Taken together, these results showed that guava leaf flavonoids had significant anti-diabetic and liver protective activities in diabetic mice. This study could facilitate the development of hypoglycemic functional foods from guava leaves.

1. Introduction

Diabetes mellitus (DM) is a complex and multifactorial disorder characterized by hyperglycemia and impaired insulin action and/or insulin secretion (Lin & Sun, 2010). The International Diabetes Federation reported that DM affected 451 million people and led to ~5 million deaths in 2017, and the worldwide prevalence of diabetes was expected to reach 693 million cases by 2045 (Cho et al., 2018). The global healthcare expenditure for diabetes treatment was predicted at USD 850 billion for 2017 (Cho et al., 2018). The available therapies for DM have been insulin and various oral antidiabetic agents, sulfonylureas, biguanides, glinides, and thiazolidinediones inhibitors, which have a lot of serious adverse effects (Vinayagam, Jayachandran, & Xu, 2016). Therefore, there is a need to develop additional strategies for treatment and prevention of these health problems. There has been evidence that dietary factors are involved in diabetic regulation and prevention (Ismail et al., 2018; Saravanan & Ponmurugan, 2013). Because of their minor side effects, interest in using components of plants as drug alternatives to treat DM has been increasing (Berná et al., 2014).

Psidium guajava L. (Myrtaceae), commonly known as guava, is an important food crop and medicinal plant in tropical and subtropical countries (Gutiérrez, Mitchell, & Solis, 2008). It is used for food and folk medicine around the world and different parts of the plant have many pharmacological properties including anti-diabetic, anti-inflammatory, anti-bacterial, anti-hypertension and anti-diarrhea activities (Lufuluabo et al., 2018; Sharma et al., 2017; Zahin et al., 2017; Zhang et al., 2016). Guava leaf has been used for treating DM, and many studies had shown its anti-diabetic effects *in vitro* and *in vivo* (Díaz-de-Cerio et al., 2017). In an *in vitro* study, the high polarity fractions of guava leaf aqueous extracts increased glucose-uptake in liver cells, resulting in alleviation of hypoglycemia in diabetic mice (Cheng, Shen, & Wu, 2009). Guava leaf aqueous extracts also promoted glucose uptake and glycogen accumulation by modulating the insulin signaling pathway in high-glucose-

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Hepatoprotective effects of *Moringa oleifera* Lam (Moringaceae) leaf extracts in streptozotocin-induced diabetes in rats

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Moringa oleifera
Diabetes
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ABSTRACT

Effects of methanolic leaf extracts of *Moringa oleifera* (MO) on hepatic injury in streptozotocin (STZ)-induced diabetes were investigated.

Male Wister rats were divided into 6 groups (n = 7). Animals in group A were orally treated daily with 3.0 ml/kg/body weight (BW) of distilled water, while B, E and F were similarly treated with 500, 250 and 500 mg/kg/BW of MO, respectively. Groups C-F were rendered diabetic by single intraperitoneal injections of 45 mg/kg/BW of STZ. Additionally, group D was treated with subcutaneous insulin (2.0 U/kg/BW, bid).

Diabetic animals exhibited significant weight loss, polydipsia, impaired glucose tolerance, fasting hypoinsulinemia and impaired liver function tests compared to controls. Treatment with MO methanolic leaf extracts significantly improved weight loss, polydipsia, glucose tolerance and also liver function tests in diabetic animals.

MO has dose-dependent antidiabetic and hepatoprotective effects.

1. Introduction

Diabetes mellitus is associated with increased morbidity and mortality globally and 425 million adults aged between 20 and 79 years were diagnosed with diabetes in 2017 (IDF, 2018; Ogurtsova et al., 2017). Due to defects in insulin secretion, insulin action, or both persistent hyperglycemia affects carbohydrate, lipid and protein metabolism (ADA, 2017). Long term complications include hepatic injury characterized by cirrhosis, inflammation, apoptosis, and microvascular and macrovascular aberrations (ADA, 2009; Hernandez et al., 2018).

Liver function tests are commonly used in clinical practice to diagnose and monitor liver diseases. Liver enzymes such as Alanine Aminotransferase (ALAT; EC 2.6.1.2), Aspartate Aminotransferase (ASAT; EC 2.6.1.1), Gama-glutamylaminotransferase (GGT; EC 2.3.2.2) and albumin are routinely used as biomarkers for hepatocyte integrity (Harris, 2005). GGT is more specific to liver injury, is responsible for the catabolism of extracellular glutathione and is elevated in conditions of increased oxidative stress and inflammation such as diabetes (Wang, Koh, Yuan, & Pan, 2016). ALAT is specific for hepatocyte necrosis and although ASAT levels may be elevated in other conditions such as heart failure or myocardial infarction, increased levels are also indicative of liver disease. The liver synthesises albumin, and hepatocellular inflammation and increased oxidative stress which are common conditions in persistent hyperglycemia are known to cause hypoalbuminemia (Levitt & Levitt, 2016). Studies have shown that the chances of damaged liver being able to heal is reduced in the acute phase which often leads to a chronic diseases with complications. In spite of considerable progress in modern medicine, there are very few therapeutic agents that can protect the liver from damage and stimulate liver functions. For these reasons, many patients with liver disease use herbal remedies to solve their health problems (Parmar, Vashrambhai, & Kalia, 2010).

It has been reported that 80% of the world's population use traditional medicines in primary healthcare due their abundance, affordability, safety and efficacy (World Health Organization, 2013). In South Africa for example, 80% of the population uses some sort of traditional medicines to meet their primary health care needs (van Wyk, 2008). One of such medicinal plants is MO which is commonly called "drumstick tree" in English, "Zogale" and "Gergedi," in Hausa and Igala languages of Nigeria, respectively (Atawodi et al., 2010). MO was first discovered in India, Asia and some parts of Western Africa in countries such as, Ghana and Senegal (Booth and Wickens, 1988). In the Limpopo province of South Africa, MO is grown by small scale farmers and the

Abbreviations: ADA, American diabetes association; ANOVA, one way analysis of variance; ALAT, Alanine Aminotransaminase; ASAT, Aspartate Aminotransaminase; AUC, areas under the curve; BW, body weight; FBG, fasting blood glucose; FPI, fasting plasma insulin; GC–MS, gras chromatography mass spectrometry; GGT, gamma glutamyl aminotransaminase; MO, Moringa oleifera; OGGT, oral glucose tolerance tests; STZ, streptozotocin

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Anti-diabetic, hepatoprotective and antioxidant potential of *Brassica oleracea* sprouts

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Anti-diabetic
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GLUT2
SGLT1

ABSTRACT

The aim of this study and experiments was to estimate the anti-diabetic and hepatoprotective effect of *Brassica oleracea* sprouts extract in streptozotocin induced diabetic rats. Diabetes is induced in rats by intra-peritoneal injection of Streptozotocin. Diabetes introduction was verified 3 days post administering Streptozotocin, when an elevated blood sugar level was observed in rats. Scheduled doses of methanolic extract of *Brassica oleracea* sprouts were given to the diabetic rats. The duration of this experiment was 28 days. Rats were made to fast overnight for oral glucose tolerance test; antioxidant parameters were also estimated. After this, these rats were euthanized for histopathological studies. One of the three doses of methanolic extract of *Brassica oleracea* sprouts showed results almost similar and sometimes even better than Glibenclamide (standard drug used for the experiment). Depletion in blood glucose level was seen after administering Broccoli extract doses. Effects on HOMA-IR and HOMA- β, plasma insulin level, glycated hemoglobin and several other parameters was seen to be positive. Also, antioxidant parameters, GLUT2 and SGLT1 showed enhancement in diabetic condition of rats. It can be inferred that methanolic *Brassica oleracea* sprouts extract had a noteworthy effect on Streptozotocin induced rats. Especially 200 mg/kg dose had an impressive results record. Elevated levels of GLUT2 and SGLT1 in rats were reduced on treatment with *Brassica oleracea* sprouts extract. This shows that our broccoli extract has a remarkable anti-diabetic effect.

1. Introduction

Alterations in lifestyle has diminished physical activity, growth of obesity, rapid variations in environmental complications which are intensifying causes of diabetes mellitus (Reaven and Reaven, 2018). Globally, an estimation is that in the year 2017 there were four hundred and fifty-one million people with diabetes all over the world (Bevir and Bevir, 2012; Lancet, 2017). These figures are expected to increase to six hundred ninety-three million by 2045. It is also approximated that almost 49.7% people are living with undiagnosed diabetes (Bagust et al., 2003; Gross et al., 2005). Furthermore, it has been evaluated that 374 million people suffer from IGT (impaired glucose tolerance) and about 21.3 million females suffered with hyperglycaemia during gestation (Karuranga et al., 2018) (Pinheiro et al., 2008). In 2017, about five million people died globally ascribable to diabetes in age ranging from 20 to 99 years (Abbott and Bakris, 2002; Hashimoto and Tanaka, 2017; Ma and Zhu, 2013). The worldwide health management disbursement on diabetic patients was calculated to be USD eight hundred and fifty billion in the year 2017 (Jamshed et al., 2018; Wong et al., 2018).

Diabetes mellitus is polygenic disorder which prevail either when the pancreas produce insulin that is insufficient for the body or when the body have lost the effectiveness of using the insulin that body has produced (Bastaki, 2005; Naderpoor et al., 2015). Insulin is a hormone that aid in controlling the level of blood glucose by indicating the liver, muscle and also fat cells for intake of glucose from blood (Cydulka and Maloney, 2012; Vuong et al., 2009). Uncontrolled diabetes leads to a condition of elevated blood glucose level that is termed as hyperglycaemia which would lead to acute damage to body organs (Gomber, 2011; Shaw et al., 2015).

Medicinal or Herbal plants are local hereditament having importance at global level (Kumar et al., 2013b)· (Nortje and Van Wyk, 2015). The world is blessed with wealth of medicinal plants (Jansen et al., 2013; Parikh et al., 2014). These plants play salient role in the

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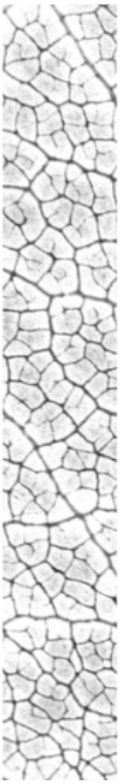

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Histopathological and Biochemical study on the effect of flavonoids isolated from the plant *Curcuma longa* effective in liver enzymes (GOT, GPT) to female rats infected eggs diabetes induced in alloxan

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Abstract
The study was conducted in Faculty of Applied Science Department of Applied Chemistry / University of Samarra the study included to recognize the effects of flavonoids isolated from a Curcuma longa plant to minimize the damage caused by diabetes induced by alloxan in the histological structure of liver and the levels of the (GOT & GPT) in liver congeneric. The experimental divided to three group each group contains five rats. The one group is control and the second group is adiabatic animal by peritoneal injection Alloxan 50 mg/kg according to body weight it has not been treated, the final group was the diabetic animals and it has been processed with Alloxan 50 mg/kg and flavonoids compound 40 mg/kg and in the final of the experiment the animal killed for anatomy liver and cut 2gm of it to do histological sections from Liver for the study and measurement the concentration of enzymatic liver GOT & GPT.

Keywords: flavonoids, alloxan, liver, GOT & GPT

Al-samarrai YHJ, Alsamarraie AMM, Fadhil MA, AL-badri BMA (2019) Histopathological and Biochemical study on the effect of flavonoids isolated from the plant *Curcuma longa* effective in liver enzymes (GOT, GPT) to female rats infected eggs diabetes induced in alloxan. Eurasia J Biosci 13: 795-801.

INTRODUCTION

The liver is an important organ (Li et al. 2015). Primary cells suffer lesions induced by oxidative stress in the liver are parenchymal (Sanchez-Valle et al. 2012). The liver works to regulate the level of glucose in the blood and the need for the body to store more animal starch with glycogen, which is converted into glucose when necessary (West 2002), and organic flavonoid compounds with a chemical structure consisting of in: Three hexagonal rings and three hydroxyl groups and two oxygen atoms, the compounds characterized the flavonoids with their inhibitory activity of certain enzymes and antioxidants (Dragan et al. 2007), and also function as a proof of the phenomenon of fat oxidation associated with diabetes and, consequently, necrosis and liver cell damage (Majumdar et al. 2008). Alloxan is a toxic glucose analog widely used to induce experimental diabetes in animals. It specifically annihilates the creator cells of insulin in the pancreas of the creatures and seems to establish a redox cycle with the disposition of superoxide radicals and undergo the decomposition of hydrogen peroxide with the development of hydroxyl radicals (Szkudelski 2001, Vanhorebeek et al. 2005, 2009). Plants have always been an exemplary source of medicines and mainly the currently available drugs have been obtained directly or indirectly from botanical products (Ojo et al. 2013). Curcuma longa is a perpetual rhizomatous herb that has a place with the family Zingiberaceae, a local of South Asia and commonly known as turmeric. In Malaysia, commonly known as Kunyit, the turmeric plant is a well-known element for preparing culinary dishes. In addition, it is used as a homegrown cure due to the common conviction that the plant has therapeutic properties. In the prescription of the society, the juice of rhizome of C. longa is used in the treatment of numerous ailments, for example, anthelmintics, asthma, gonorrhea and urine, and its essential oil is used in the treatment of carminatives, stomachs and tonics (Phansawan and Poungbangpho 2007). In traditional medicine, several plants and herbs have been used experimentally to treat liver disorders, including liver cirrhosis (Alshawsh et al. 2011). C. longa possesses antioxidant (Maizura et al. 2011), anti-tumor (Kunnumakkara et al. 2007), antimicrobial (Kim et al. 2005), anti-inflammatory (Kohli et al. 2005), wound

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Original article

Hepatoprotective effect of *Opuntia microdasys* (Lehm.) Pfeiff flowers against diabetes type II induced in rats

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ABSTRACT

Opuntia sp. has long been used as a folk medicine to treat hepatitis and diabetes in Sicile (Italy). To extract the polyphenols from the flower of *Opuntia microdasys* Lehm. at post flowring stage and evaluate the antidiabetic activity *in vitro* and *in vivo*. The hepatoprotective activity of *Opuntia microdasys* aqueous flowers extract at post flowering stage (OFP) has been tested for their antidiabetic activity. On fructose-alloxan induced diabete in rat model, evaluating the inhibitory effects of OFP on some carbohydrate metabolizing enzymes, pancreatic α-amylase and intestinal α-glucosidase activities *in vitro*. The OFP extract showed inhibitory activity against α-glucosidase (IC_{50} = 0.17 ± 0.012 mg/ml) and α-amylase (IC_{50} = 2.55 ± 0.41 mg/ml). The inhibitory potential of OFP extract on these enzymes suggests a positive and probable role of this extract in the management and treatment of diabetes mellitus, particularly, for type 2. Oral administration of the OFP at 200 mg/kg to diabetic male rats for 28 days demonstrated a significant protective effect by lowering the levels of glucose (123.21 ± 1.38 mg/dL) and hepatic marker enzymes (AST, ALT, LDH, γ-GT, BT, PAL, TC, LDL-C, HDL-C and TG). OFP attenuated oxidative stress by decreasing the SOD, CAT, GP_X activity and the levels of PC and MDA in the liver and restored the histological architecture of the rat liver. OFP has protective effects on the protection of liver, thereby reducing some of the causes of diabetes in experimental animals.

1. Introduction

Diabetes mellitus is one of the major global public health problems. The total number of diabetic peoples was estimated to increase from 171 million in 2000 to 366 million in 2030 and most of these will be dominated by those suffering from type 2 diabetes (95% T2D) [1,2]. T2D is a heterogeneous disorder, characterized by a progressive decline in insulin action (insulin resistance-IR), followed by the inability of pancreatic β-cells to compensate for IR (β-cell dysfunction) [3]. Fructose feeding leads to insulin resistance and compensatory hyperinsulinemia responses [4]. Fasting hyperglycemia is caused by unrestrained basal hepatic glucose output, primarily as a consequence of hepatic resistance to insulin action [5]. Synthetic hypoglycemic agents produce serious side effects, whereas bioactive compounds derived from natural resources are frequently considered safe and cost effective [6]. Thus, plants may play an important role in drug development programs. There is a growing interest among researchers to discover new and effective α-glucosidase inhibitors with minimal side effects, from medicinal plants with known and scientifically proven antidiabetic properties [7,8]. For this reason, the use of natural treatments from food or medicinal plants is considered to be effective and safe for hepatotoxicity, mainly because of the presence of various antioxidant compounds (flavonoid and phenolic acid compounds, etc.). The Cactus (*Opuntia* sp.) has often been used in traditional folk medicine (Cactus pear cladodes, fruits and flowers) for treatment of a great number of diseases and pathological conditions, such as diabetes, stomach ulcers, renal diseases, etc. [9,10]. For example, the traditional Sicilian medicine

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Moringa concanensis Nimmo extracts ameliorates hyperglycemia-mediated oxidative stress and upregulates PPARγ and GLUT4 gene expression in liver and pancreas of streptozotocin-nicotinamide induced diabetic rats

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ABSTRACT

The current study investigates the effects of ethanolic extract of *M. concanensis* Nimmo leaves (EEMCNL) with respect to its potent protective tissue damage, antioxidant properties in serum, liver and kidney, histopathological evaluation, and PPARγ and GLUT4 gene expression in liver and pancreatic tissue of Streptozotocin-Nicotinamide (STZ-NA) induced diabetic rats. Animals were divided into five groups (n = 5): control; diabetic; diabetic + EEMCNL; control + EEMCNL; and diabetic + glibenclamide. After 45 days of treatment with EEMCNL, MDA levels were significantly decreased in the diabetic-induced group when compared with the STZ-induced diabetic group ($P < 0.05$). The activities of serum enzymes AST, ALT, ALP, ACP and LDH were significantly decreased in serum and kidney, and increased in liver tissues of the EEMCNL-treated group as compared with the STZ-NA induced diabetic group ($P < 0.05$). The levels of total protein, urea, creatinine and uric acid observed in the diabetic group returned to normal by administration of EEMCNL (250 mg/kg) as relative to the STZ-NA induced diabetic group ($P < 0.05$). Furthermore, EEMCNL upregulated PPARγ and GLUT4 expression in liver and pancreatic tissue of the STZ-NA induced diabetic group rats. Taken together, these findings contribute to a better understanding of the hepatoprotective and renoprotective potential of EEMCNL against oxidative stress in the diabetic state, which was evidenced by the capacity of EEMCNL to modulate the antioxidant defence and to decrease lipid peroxidation in these tissues.

1. Introduction

Diabetes mellitus is a serious metabolic disorder. It is characterised by hyperglycemia which is associated with glucose intolerance, carbohydrate, fat and protein metabolism resulting from damaged pancreatic β-cells and/or insulin secretion/deficiency. Hyperglycemia is usually associated with several illnesses including polydipsia, polyurea, polyphagia, weight loss and reduced ability to fight infection. The long-term hyperglycaemic diabetic condition may lead to several complications including cardiovascular, neurological, renal and ocular diseases [1]. Insulin resistance causes increased glucose uptake and utilisation in skeletal muscle and adipose tissue due to reduced GLUT4 levels [2,3]. According to the World Health Organization (WHO), 422 million people are expected to develop diabetes mellitus in both developed and developing countries due to their lifestyle and food habits [4]. Hyperglycemia produces reactive oxygen species (ROS), which play a fundamental role in the complication of diabetes. The exact cellular and molecular mechanism of oxidative stress and pathogenesis of diabetes is still not fully understood. However, elevated glucose levels can increase non-enzymatic, auto-oxidative glycosylation, polyol and hexosamine pathways, as well as increased protein kinase C activity, leading to reductions in both inflammatory mediators and antioxidant defence. These pathways are mainly involved in ROS production in the diabetic state, which directly increase oxidative stress in various organs and tissues [5,6].

In addition to pancreatic β-cells, the increased amounts of glucose

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ARTICLE

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The Protective Effect of Hydroalcoholic Extract of *Rosa canina* (Dog Rose) Fruit on Liver Function and Structure in Streptozotocin-Induced Diabetes in Rats

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ABSTRACT

This study was conducted to evaluate the hepatoprotective effects of *Rosa canina* (*R. canina*) extract on streptozotocin- (STZ-) induced diabetes in rats by measuring the fasting blood glucose (FBG), total antioxidant capacity (TAC), and liver enzyme activity, including serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Forty adult male Wistar rats were randomly divided into four groups and treated daily for 42 days as follows: group I (control) received saline as a vehicle; group II (diabetic) received saline; groups III and IV (diabetic) treated with 250 and 500 mg/kg body weight (BW) per day *R. canina* extract, respectively. Diabetes was induced by a single intraperitoneal (IP) injection of streptozotocin (50 mg/kg BW). At the end of the study, blood samples were collected via heart puncture and sera were used for estimation of the mentioned parameters. Then all the rats were sacrificed and their livers used for histopathological evaluations. In the untreated diabetic group, the results showed a significant increase in FBG, ALT, and AST levels compared to the other groups ($p < .05$). The level of TAC decreased in this group, but not significantly compared to the other groups ($p > .05$). In the treated groups, administration of *R. canina* extract significantly improved the mentioned parameters in a dose-dependent manner ($p < .05$). Histological evaluations indicated that *R. canina* extract ameliorated defective liver caused by STZ. It can be concluded that *R. canina* extract has a hepatoprotective effect in STZ-induced diabetes in rats.

KEYWORDS

diabetes mellitus; hepatoprotective; *Rosa canina*; streptozotocin

Introduction

Diabetes mellitus includes a group of chronic metabolic disorders characterized by hyperglycemia frequently accompanied by polydipsia, polyuria, and glycosuria. The disorder develops due to disturbance in insulin secretion or function or both, and is associated with specific changes in intracellular metabolism and function in a large number of tissues, such as liver (Hashempur et al., 2015; Heydari et al., 2016). Hyperglycemia, hyperlipidemia, and decreased

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Research Article

Hepatoprotective Potential of *Sargassum muticum* against STZ-Induced Diabetic Liver Damage in Wistar Rats by Inhibiting Cytokines and the Apoptosis Pathway

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Liver inflammation and necrosis are the foremost problems interlinked with diabetes mellitus (DM). The methanolic extract of *Sargassum muticum* (MESM) plays a hepatoprotective role in streptozotocin- (STZ-) induced hepatic injury. In this study, STZ exposure induced diabetes that augmented hepatic damage, which was reflected in serum enzyme markers, the cytokine network, and caspase-3 and caspase-9 levels in Group 2. Exposure to the MESM tremendously modulated the levels of hepatic enzyme markers ALP, ACP, ALT, and AST in Groups 3 and 4. The cytokine network was well regulated by suppressing the release of cytokines, and the levels of caspase-3 and caspase-9 were also reduced in Groups 3 and 4. The present study suggests that MESM treatment at 200 and 500 mg protected the liver and also minimizes the glucose level. Thus, the MESM plays a key role in rejuvenating the liver and can modulate diabetes's pathogenic effect by reducing the glucose level.

1. Introduction

Diabetes mellitus is a metabolic disorder that has developed into a global life-threatening disease; it is characterized by polyphagia, polydipsia, polyuria, blurred vision, and weight loss [1]. Scientific reports show that diabetes mellitus is associated with liver damage or abnormalities leading to acute liver disease [2]. The prevalence of chronic liver disease has been anticipated in the next decade due to metabolic syndrome whose symptoms include abdominal obesity as well as insulin resistance [3]. Insulin resistance is one of the vital causes of type 2 diabetes mellitus and leads to a hyperglycemic state and oxidative stress, causing liver tissue necrosis [4–6]. A healthy liver regulates its cellular growth and function by the homeostatic mechanism, conserving persistent tissue mass compared to levels of metabolic stress in the body. The liver plays a predominant role in regulating glucose homeostasis, suggesting evidence of pathogenesis of glucose intolerance in diabetes mellitus. Research studies have shown that diabetes mellitus is caused by oxidative stress that leads to the production of reactive oxygen species (ROS), which are the major causes of cellular damage [5, 7]. Therefore, diabetes mellitus is highly related to liver inflammation, cirrhosis, apoptosis, and β-cell dysfunction, and it ultimately causes liver malfunction. Seaweed is a potential resource of bioactive compounds, and their properties are well known across the world [8]. *Sargassum muticum* is an olive-brown alga which grows in the infralittoral zone on rocks, stones, and shells. Furthermore, *Sargassum muticum* is a very common seaweed in the Red Sea of Jazan Province, KSA, and its biological and pharmaceutical properties have not yet been explored. Thus, the present study's objective was to explore the hepatoprotective effect of the seaweed's extract and

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ORIGINAL RESEARCH

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Hepatoprotective effects of flavonoids from common buckwheat hulls in type 2 diabetic rats and HepG2 cells

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Abstract

Flavonoids from common buckwheat hulls (BHFs) show significant antioxidant and antidiabetic potential. However, their hepatoprotective property is yet to be defined. This study aims to examine the hepatoprotective effect of BHFs in type 2 diabetes mellitus (T2DM) rats and chronic high glucose-damaged HepG2 cells. Results showed that BHF treatment significantly relieves the state of insulin resistance, thereby reducing blood glucose and improving oxidative stress in T2DM rats. It is worth mentioning that BHF treatment improved diabetes-induced liver damage disorders, manifested as the clearance of liver fat and the decline of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities. In vitro, HepG2 cells pretreated with BHFs maintained higher superoxide dismutase (SOD), glutathione peroxidase (GSH-px), and catalase (CAT) activities than the unprotected group. In parallel, compared with the unprotected group, BHFs significantly reduced the leakage of ALT and AST in pre-protected group dose-dependently. These results indicated that BHFs had considerable antioxidant and hepatoprotective potential and could be promising to be used as nutraceuticals and dietary supplements to prevent and/or protect against liver disorders.

KEYWORDS

antioxidant, buckwheat hull flavonoids (BHFs), hepatoprotective potential, HepG2 cells, type 2 diabetes

1 | INTRODUCTION

Common buckwheat is one of the most commonly cultivated grain species across the globe. Large amounts of buckwheat hulls are produced during its processing as a by-product. Numerous studies reveal that buckwheat hulls are embedded with rich amounts of flavonoids, which include but are not limited to, rutin, vitexin, quercetin, isoorientin, and hyperoside (Cui et al., 2020; Dziadek et al., 2016; Zhang et al., 2017). Flavonoids are the most studied subclass of polyphenolic compounds that are present in almost all parts of flowering plants, such as grains, fruits, vegetables, and teas (Cassidy & Minihane, 2017; Swallah et al., 2020), with more than 9,000 identified different structures bearing similar diphenol propane skeleton in nature (C6-C3-C6) (Swallah et al., 2020). Flavonoids are well evidenced in numerous studies as the widest subclass with hydrosoluble heterocyclic

Lampiran. 14 (Jurnal 14)

Hyperglycemia, oxidative stress, liver damage and dysfunction in alloxan-induced diabetic rat are prevented by *Spirulina* supplementation

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Protective Effect of Ethyl Acetate Fraction of *Stereospermum Suaveolens* Against Hepatic Oxidative Stress in STZ Diabetic Rats

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ABSTRACT

Stereospermum suaveolens is a folk remedy for the treatment of diabetes and liver disorders in southern parts of India. In the present study, the protective effect of the ethyl acetate fraction of ethanol extract from *S. suaveolens* against hepatic oxidative stress was evaluated in streptozotocin (STZ)-induced diabetic rats for 14 days. The ethyl acetate fraction was administered orally to the STZ diabetic rats at the doses of 200 and 400 mg/kg. Blood glucose level was measured according to glucose oxidase method. In order to determine hepatoprotective activity, changes in the levels of serum biomarker enzymes such as aspartate transaminase (AST), alanine transaminase (ALT), and serum alkaline phosphatase (SALP) were assessed in the ethyl acetate fraction treated diabetic rats and were compared with the levels in diabetic control rats. In addition, the antioxidant activity of ethyl acetate fraction was evaluated using various hepatic parameters such as thiobarbituric acid reactive substances (TBARS), reduced glutathione (GSH), superoxide dismutase (SOD), and catalase (CAT). It was found that administration of ethyl acetate fraction (200 and 400 mg/kg) produced a significant ($P < 0.001$) fall in fasting blood glucose level, TBARS, bilirubin, AST, ALT, and SALP, while elevating the GSH levels, and SOD and CAT activities in diabetic rats. Histopathologic studies also revealed the protective effect of ethyl acetate fraction on the liver tissues of diabetic rats. It was concluded from this study that the ethyl acetate fraction from ethanol extract of *S. suaveolens* modulates the activity of enzymatic and nonenzymatic antioxidants and enhances the defense against hepatic oxidative stress in STZ-induced diabetic rats.

Key words: Antioxidant enzymes, Ethyl acetate fraction, Histopathology, Serum biomarker enzymes, *Stereospermum suaveolens*, STZ-induced diabetic rats

INTRODUCTION

Diabetes mellitus is a multifaceted serious illness involving endocrine pancreas with multiple complications and affecting more than 285 million people worldwide, and is considered as one of the three leading causes of death in the world.[1] In diabetes, oxidative stress has been found to be mainly due to an increased production of reactive oxygen species and a sharp reduction of antioxidant defenses.[2] A number of clinical studies suggest that the antioxidants in plants are key factors in reducing the incidence of diabetic complications.[3,4] Finding new natural sources of antioxidants with potential antidiabetic activity can be useful to

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