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Research Article

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In-vitro and *in-vivo* anti-hyperglycemic activity of methanolic extract of *Arbutus pavarii* Pampan and *Sarcopoterium spinosum* L. growing in Libya

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Abstract

The aim of the study was to evaluate the *In-vitro* and *In-vivo* effects of methanolic extracts of the aerial parts of ***Arbutus pavarii*** Pampan (APME)and ***Sarcopoterium spinosum*** L. (SSME) on α-glucosidase and the fasting blood glucose levels (FBG) of insulin using Streptozotocin-induced diabetic rats model. The levels of other biochemical parameters were also measured to assess the effect of these extracts on liver and kidney functions. The plant materials were exhaustively extracted by maceration with methanol. The results revealed that the SSME showed higher α-glucosidase inhibitory activity than APME when compared with the standard inhibitor acarbose. Although the fasting blood sugar level was reduced significantly by the oral administration of SSME and APME, the extract caused a significant increase in the serum insulin level. The administration of SSME and APME had significantly reduced the serum levels of aspartate aminotransferase and alanine aminotransferase compared with the diabetic untreated rats. SSME increased the levels of the antioxidant enzymes such as glutathione, glutathione peroxidase, catalase, and superoxide dismutase almost back to normal amounts followed by APME in contrast to the diabetic control rats.

Keywords: ***Arbutus pavarii*** Pampan, ***Sarcopoterium spinosum,*** α-glucosidase, antioxidant, serum insulin.

1. Introduction

Metabolic disorders that interfere with the ability of the body to produce or respond to insulin may lead to diabetes mellitus. This results in several disturbing effects and complications; including neuropathy, nephropathy, retinopathy, hyperthyroidism, hypertension, arteriosclerosis, and many other serious conditions [1, 2, and 3]. There are many drawbacks associated with antidiabetic conventional drugs that can lead to various long-term problems [4].Therefore, In order to achieve full control of hyperglycemia with minimal side effects, herbal medicine should be utilized [5]. The investigation on medicinal plants typically depends on extraction techniques as they can profoundly determine the properties of the obtained extracts, such as yields percentage and the quality of the produced phytochemicals [6].

Several herbs have been used as a food and extensively employed in the treatment of numerous diseases without the proper knowledge of their characteristics and functions. Although phytotherapy is still widely used in different countries, few plants have been subjected to a scientific or medical examination [7].

Furthermore, plants could provide a great chance to discover new natural medicinal molecules. Some of these compounds may have beneficial effects on glucose homeostasis in diabetics without causing any unwanted effects currently observed in modern antidiabetic agents [7-10].

The search for medicinal herbs and their active phytochemicals to find alternative treatment of diabetes can also provide other benefits such as maintaining normal blood pressure, preventing heart problems, enhancing the antioxidant mechanisms as well as insulin secretion and action [11]. Phyto-constituents have always been the base of the discovery and development of new drugs. Hence, there is a continuous research for antioxidant compounds of natural origin that can control blood sugar levels [12].

Arbutus pavarii Pamp. (Ericaceae) and *Sarcopoterium spinosum* L. (Rosaceae) are of the most important endemic plants in El-Jabel El-Akhdar, as they have thoroughly described in the Libyan flora [13].Several bioactive agents were isolated from *A. pavarii* Pamp such as arbutin, ferulic acid, Kampferol- O- β- D- rutinoside, catechin, methyl gallate [14,15], and *pyrogallo*, while catechin and *E-vanillic acid* was the main component found in *S. spinosum*[16].

Accordingly, both plants are considered as a valuable source of effective constitutes, especially catechin, which has been reported to be associated with hypoglycemic effects and showed interesting α-glucosidase inhibitory activity [17].

2. Materials and Methods

Preparation of plant extracts

Constant weight of the aerial parts of each plant (250g) was dried in the open air and separately grounded into smaller pieces, homogenized in a mixer then soaked in boiling methanol 90% for 30 minutes (to deactivate enzymes). Extraction was carried out by maceration in methanol 70% until exhaustion. The collected methanolic extracts were evaporated under reduced pressure at a temperature not exceeding 50^{o}C to yield 30g.

Chemicals

(Streptozotocin) STZ (Sigma-Aldrich, Egypt), glibenglamide (Sigma Co., USA) was used as anantidiabetic standard drug. Biodiagnostic transaminase kits for aspartate aminotransferase (AST), alanine aminotransferase (ALT), Oxidative stress and insulin kits (Bio-merieux Co., France) were used for the assessment of different biological effects of extracts. Glucose Kits: Biodiagnostic for the measurement of glucose level, α-glucosidase enzyme (Sigma-Aldrich, Egypt), substrate p-nitrophenyl-α-D-glucopyranoside (p-NPG, 1mM) (Sigma-Aldrich, Egypt), Na2CO3 (1 M, 1mL) (Sigma-Aldrich, Egypt) and Acarbose (Sigma-Aldrich, Egypt).

Enzyme Inhibition Assay

The enzyme Inhibition analysis was performed by α-glucosidase inhibition assay according to Kee *et al*. method with some modifications [18].α-Glucosidase is an enzyme that catalyzes the final step in the carbohydrates digestive process [19].

Briefly, α-glucosidase enzyme (0.1U/mL) and substrate p-nitrophenyl-α-D-glucopyranoside (p-NPG, 1mM) were dissolved in potassium phosphate buffer (0.1M, pH 6.7); all samples were then dissolved in DMSO at a concentration range of 0.1-50mg/ml. The enzyme (100µL) were incubated in 96-well flat-bottom micro-plate with the samples at 37C° for 10 min, after that a substrate (200µL) was added to the mixture to allow the enzymatic reaction for 30min. Na2CO3 (1M, 1mL) was added to terminate the reaction; the absorbance was recorded at 405nm. All test samples were analyzed in triplicate with multipleconcentrationstocalculatetheIC50 values. Acarbose was used as a reference compound.

The findings were expressed as percentage inhibition. The following equation is used for the calculation:

$$\text{Inhibition (\%)} = \frac{(Ac-Acb)-(As-Asb)}{Ac-Acb} \times 100$$

Where Acb is the absorbance of the control blank (buffer without enzyme), Ac refers to the absorbance reading of the control (enzyme and buffer), As is the absorbance of the sample (enzyme and inhibitor), while Asb is the absorbance of the sample blank (inhibitor without enzyme).

Experimental animals:

Adult male albino rats of Sprague Dawley strain (130-150g) were used for the assessment of the antidiabetic activity of the extracts. The animals were kept for at least one week under controlled laboratory conditions before starting the experiments. The rats were fed on water and a standard pellet diet composed of mineral mixture (4%), corn oil (10%), sucrose (20%), vitamin mixture (1%), cellulose (0.2%), casein (10.5%), and starch (54.3%).

Overnight-fasted rats were injected intraperitoneally with freshly prepared STZ (50mg/kg, dissolved in 0.1M cold citrate buffer, pH 4.5) to induce diabetes. They were tested for successful induction of diabetes every two, five, and seven days after STZ injection by measuring FBG levels. Only rats with blood glucose levels over 250mg/dl were enrolled in the study.

Five groups of animals (ten each) were used, the doses of the methanolic extracts were determined by **Ferreira *et al.* 2012** [20] and **Kasabri *et al.* 2011** [21] for *A. pavarii* Pampan and *S. spinosum* L respectively.

Group-1 were healthy (non-diabetic) rats to serve as the normal control group, they received distilled water.
Group-2-5were STZ diabetic rats.
Group-2 served as diabetic-untreated control receiving only distilled water.
Group-3 received APME (500mg/kg dose)
Group-4 were given SSME (600mg/kg dose)
Group-5were given glibenclamide (2.5mg daily dose).

Animals administered the oral treatments once a day for four weeks, starting from 8th day after induction of diabetes. The crude extracts under investigation were suspended in water. The change in FBG and the improvement in glucose tolerance were observed at the end of each week. Blood samples were drawn to be used for the determination of FBG, insulin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), glutathione peroxidase (GSPx), reduced glutathione (GSH), superoxide dismutase (SODs), catalase and malonaldehyde (MDA).

Statistical analysis

IBM SPSS® software platform was used to obtain the P-value by applying One-Way ANOVA analysis.

3. Results

In-vitro antidiabetic activity

As displayed in Table 1, the α-glucosidase suppression potential of acarbose (IC50) was 0.789±0.012mg/ml, compared with control incubations. APME exhibited α-glucosidase inhibitory activity at the concentration (1.076±0.002mg/ml) comparable to the approved acarbose drug. However, SSME showed higher inhibitory activity at the same concentration in contrast to APME.

Table 1: Result of the *in vitro* α-glucosidase inhibitory assay of APME and SSME

Type of extract	IC_{50} (mg/ml)
APME	1.076± 0.002
SSME	0.902±0.3
Acarbose	0.789±0.012

In-vivo antidiabetic activity

1- Effect of oral treatments of extracts on fasting blood glucose level (FBG)

As presented in table 2, administration of 500mg/kg and 600mg/kg doses of APME and SSME respectively by diabetic rats for two weeks resulted in a significant decrease of FBG levels from 360mg/dl to 250.4mg/dl for *A. pavarii* Pampan L. while dropped from 426.7mg/dl to 129.8mg/dl for *S. spinosum* L. The percentage of blood glucose level reduction with the same doses of both extracts recorded after four weeks (71% for *A. pavarii* Pampan L. and 75% for *S. spinosum* L.).

Table (2): Effect of (APME) and (SSME) on the level of the fasting blood glucose:

FBG	Normal Control	Diabetic	Diabetic+ Glibenclamide	Diabetic+ APME	Diabetic+ SSME
Zero	94.6±23.6	390.5±56.7	357±34.6	360.6±25.4	426.7±25.6
Week 2	95.88±26.7	450.8±44.6	140±36.7	250.4±44.7	129.8±36.7
Week 4	92.61±15.41	493.8±57.16	105.4±20.81	139.2±45.34	122.0±44.47

*Values are presented as mean ± SE of 9-test sample observations, P <0.05

2- The effect of oral treatments of extracts on serum insulin level

From table 3, it was confirmed that, the oral administration of APME (500mg/Kg b.wt.) and SSME (600mg/Kg b.wt.) extracts caused a significant increase ($p<0.01$) in insulin serum level (4.153±0.46 and 4.592±0.52 respectively) compared with the untreated diabetic rats (1.945±0.10). The increase in insulin level caused by plant extracts was comparable to that of glibenclamide.

Table (3): Effect of APME and SSME on serum insulin level

serum insulin level µIU/ ml	Normal Control	Diabetic	Diabetic+ glibenclamide	Diabetic+ (APME)	Diabetic+ (SSME)
Number of rats	9	6	8	8	7
After 4weeks	5.530±0.029	1.945±0.10	4.950±0.12	4.153±0.46	4.592±0.52

*Statistically significant from the diabetic control at p<0.1

3- The effect of extracts on liver enzymes

The effects of methanolic extract of *Arbutus pavarii* Pampan and *Sarcopoterium spinosum* L. on the biochemical parameters of diabetes-induced rats were evaluated; serum AST and ALT levels were determined to assess the hepatic functions. The treatment of the animals with STZ resulted in dramatic elevations in AST and ALT serum levels in contrast to control values and diabetic rats treated by glibenclamide.

The administration of *Arbutus pavarii* Pampan and *Sarcopoterium spinosum* L. extracts significantly reduced the AST (58% and 75% respectively) and ALT (65% and 69% respectively) serum levels when compared with diabetic untreated rats, as shown in the table 4.

Table (4): Effect of (APME) and (SSME)] on liver enzymes

Liver enzymes	Normal Control	Diabetic	Diabetic+ Drug	Diabetic+ (APME)	Diabetic+ (SSME)
AST	24.38±1.252	116.0±26.71	26.78±2.696	48.15±5.311	29.40±5.470
ALT	27.30±2.54	106.8±23.6	29.75±2.36	37.88±11.66	32.93±8.49

4 - The effect of extracts on the level of oxidative stress

The level of oxidative stress was assessed in diabetic rats by evaluating the potential of them ethanolic extract to restore various antioxidant defense systems (the levels and/or activities of GSH, GSHPx, CAT, and SOD).

Table 5: Radical scavenging activity of (APME) and(SSME)

Antioxidant enzymes	Control	Diabetic	Diabetic+ drug	Diabetic+ *A.pavarii*	Diabetic+ *S.spinosum*
GSH (µM)	93.8±1.7	48.8±7.9	90.2±1.7	75±2.8	85.9±0.7
GSHPx (U/ml)	0.965±1.4	0.243±0.25	0.922±0.43	0.786±0.21	0.884±0.13
CAT (U/mg protein)	15.31±0.98	6.4±0.43	14.2±0.74	10.1±0.32	13.85±0.43
SOD (U/mg protein)	65.5±0.14	34.65±0.65	61.23±0.65	50.98±0.76	58.45±0.24

*Values are Mean±SD, n=10 for each group ** P< 0.05, compared with control

Table 5 shows that the induction of diabetes by STZ reduced the level of the antioxidant enzymes by (47%, 74%, 58%, and 47%) for GSH, GSHPx, CAT, and SOD respectively when compared with control. SSME increased the levels of antioxidant enzymes such as GSH, GSHPx, CAT, and SOD almost back to the normal levels (43%, 72%, 53%, and 42% respectively) when compared with the diabetic untreated rats followed by APME (34%, 69%, 36%, and 42% respectively) during the four weeks.

4. Discussion

The ideal management of diabetes is the control of postprandial hyperglycemia and blood glucose level without causing hypoglycemia, hyperinsulinemia, or body weight gain. Amylase and α-glucosidase inhibitors are oral anti-hyperglycemic agents used to compensate for the rapid increase of blood glucose level after meals [22, 23].

In this research, the antidiabetic properties of *Sarcopoterium spinosum* L. and *Arbtuspavarii* Pampan extracts were evaluated *in vitro* by applying *α-Glucosidase* inhibition assay while male rats were employed *in vivo* study to measure the effects exerted on the fasting blood glucose and serum insulin levels.

Both plants exhibited significant α-glucosidase inhibitory properties, however, *A.pavarii* Pampan revealed a lower potential. Similar studies [23, 24] confirmed that SSME had a reliable inhibitory effect on α-glucosidase activity. In the present study, the *in vivo* effects of both extracts on fasting blood glucose and serum insulin levels showed results comparable to control treatment (glibenclamide). Moreover, SSME manifested *in vivo* potential superior to APME at reducing fasting blood glucose and stimulating insulin release. Several researches proved that *S. spinosum* L. has antidiabetic activity [24-28]. **Rozenberg & Rosenzweig, (2018)** indicated that an extract of *S. spinosum* L. (70mg/day) for 6 weeks enhanced insulin sensitivity and glucose tolerance in mice fed on a high-fat diet[25]. Another study by **Wollman *et al.* (2019)** stated that *S. spinosum* L. extract has a dose-dependent effect (<90 mg/day) to decrease body weight and improve insulin resistance, leading to lower levels of blood sugar[29]. Furthermore, **Smirin *et al.* (2010)** found that *Sarcopoterium spinosum* L. extract increases insulin secretion *in vitro* using rat pancreatic *β*-cells (RINm Insulinoma cells) and significantly lowers fasting blood glucose levels *in vivo* using genetically diabetic mice model (KK-Ay strain mice) [26]. Throughout this study, APME exerted a significant effect at reducing fasting blood glucose and elevating serum insulin level *in vivo*, while it resulted in a considerable *in-vitro* inhibitory property on *α-Glucosidase* activity *in vitro*. However, there is very limited literature supporting the antidiabetic effects of *Arbutus pavarii* Pampan.

The suggested mechanisms by which *S. spinosum* L. reduce blood glucose were believed to be due to its flavonoids contents (Catechin and epicatechin). These polyphenolic compounds may act as insulinosecrétagogues and/or insulinomimetics, that have similar effects to insulin and beneficial outcomes on insulin-resistance, which provide the basis for the anti-hyperglycemicproperties [15,16,26,30,31]. These flavonoids may also have the capacity to inhibit *α-glucosidase in vitro,* which can disturb carbohydrate digestion and limit glucose production[32].

The screening of both *A. Pavarii* Pampan and *S. spinosum* L. [15,16,33,34] extracts revealed the presence of flavonoids, tannins, and triterpenes. According to **Reher *et al.* (1991)**, a combination of tannins and triterpenes fractions of *Sarcopoterium spinosum* L. caused a statistically significant reduction in blood glucose level in mice, while the Catechin fraction revealed no activity[33]. The observed antidiabetic characteristics of the extracts could be attributed to the combined activity of these constituents.

Fatty liver is a condition that is usually related with type 2 diabetes (T2D) [25]. Oxidative stress of fat and lipid peroxidation in the liver can lead to hepatic injury and elevate the level of specific enzymes in the serum, which may serve as biological markers forT2D in various populations[35,36].In the present investigation, the tested APME and SSME significantly reduced AST (75% and 58% respectively) and ALT (69%

and 65% respectively) serum levels. Several studies [37,38] stated that *A. pavarii* and *S. spinosum* L. have hepatoprotective properties in animals exposed to carbon tetrachloride, as they confirmed the reduction in serum levels of ALT and AST. Another work by Wollman *et al.* (2019) demonstrated that *Sarcopoterium spinosum* L. extracts prevented the development of steatohepatitis in the experimental mice by normalizing the expression of antioxidant genes [29].

Chronic oxidative stress can result in impaired β-cell functioning in type 2 diabetes that eventually leads to low production of insulin and fasting hyperglycemia [39]. Therefore, the balance of the antioxidants defense system is a crucial mechanism to protect against T2D. Glutathione, superoxide dismutase, catalase (CAT), and glutathione peroxidase are the main enzymes that scavenge the free radicals and ROS. In this study, the level of oxidative stress in diabetic rats and the capacity of methanolic extract of the plants under examination to restore antioxidant defense systems were evaluated. The induction of diabetes by STZ caused a decline in the levels of the antioxidant enzymes by (47%, 74%, 58%, and 47%) for GSH, GSHPx, CAT, and SOD respectively, compared with the control. The SSME increased the levels GSH, GSHPx, CAT and SOD almost back to the normal levels (43%, 72%, 53%, and 42% respectively) in contrast to the diabetic untreated rats. However, APME showed less antioxidant activity in comparison with SSME, while increased the levels of antioxidants by (34%, 69%, 36%, and 42% respectively). Previous researches indicate that SSME contains antioxidant substances (e.g. phenols and flavonoids) that can protect the pancreas against the cytotoxic effect of STZ and regenerate damaged β-cells [15, 16, 31]. The scavenging activity of both *A. pavarii* and *S. spinosum* L. mainly originates from its high levels of total polyphenols and flavonoids.

5. Conclusion

This study revealed that methanolic extracts of the aerial parts of ***Arbutus pavarii*** Pampan (APME) and ***Sarcopoterium spinosum*** L. (SSME) had significant antidiabetic and antioxidant activities as determined by *in-vitro* and *in-vivo* assays. Thus, both plants can be used as a potential source for the isolation of natural bioactive molecules.

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