

Original Research

The effect of Purslane and *Aquilaria malaccensis* on insulin-resistance and lipid peroxidation in High-fructose diet Rats

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Abstract

Introduction: The aim of the present study was to evaluate the effect of purslane (*P. oleracea*) and *Aquilaria malaccensis* (*A. malaccensis*) methanol extracts against high-fructose and high-fat diet induced insulin-resistance, lipid peroxidation and tissues dysfunction in rats. **Material and Method:** Females albino Wistar rats were divided into six groups (n=5) as control, Insulin resistance rats (IR), IR+Po, IR+Am, IR+Po+Am and IR+Met groups. Insulin resistance (IR) in rats was induced by diet with a high fructose (60% fructose) and a high fat diet (60% kcal fat) for 70 days. *P. oleracea* (Po) and *A. malaccensis* (Am) methanol extracts and metformin drugs were supplemented orally (400 mg/kg bw, 200 mg/kg bw, and 300 mg/kg bw), respectively, for four weeks. Methanol extracts of plants were prepared and phytochemicals were analyzed by standard methods. Blood glucose level, lipids profile, lipid peroxidation and some biochemical parameters were assessed. **Results:** Obtained results revealed that IR induction caused a significant increase in blood glucose, plasma and tissues lipids profile, urea and creatinine concentrations, GOT, GPT, and ALP activities compared to the control group while total protein concentration was significantly lower. Additionally, there was a significant increase of MDA level in IR group than those of the control. Methanol extracts of *P. oleracea* and *A. malaccensis* treatment ensured a partial correction of the previous parameters. **Conclusions:** The results of the present investigation indicated that *P. oleracea* and *A. malaccensis* possesses the ability to control the lipid peroxidation and biochemical disruption associated with insulin resistance.

Keywords: *A. malaccensis*, High Fructose Diet, Insulin-resistance, *P. oleracea*, Rats.

Introduction

Insulin resistance is a common feature of metabolic diseases and is the leading cause of type 2 diabetes (T2D). The prevalence of T2D worldwide is extremely high (8.8% of the world population) and is growing rapidly. In 2015, T2D killed about 5 million people [1]. The pre-diabetic state preceding T2D is characterized by obesity, insulin resistance and as it has been demonstrated during in the last decade, chronic low-grade inflammation [2], is manifested by a progressive increase in insulinemia due to a lack of insulin signaling in

target metabolic organs, such as the liver, muscle and adipose tissue [3]. Insulin resistance can be broadly defined as insulin-reduced cellular reactivity, characterized by higher insulin levels needed to maintain peripheral glucose levels [4]. Nutrition characterizes a lifestyle element that can be measured, and that can directly impact health; consequently, defensive nutrition and weight control should develop a main focus of consumers and prepared-food providers [5]. Food imbalance is a major risk factor for many pathologies such as cardiovascular diseases, diabetes and obesity [6]. Oxidative stress is an important pathogenic mechanism of



the metabolic syndrome associated with insulin resistance and plays a crucial role in the pathogenesis of various diseases [7]. Current treatment, particularly with metformin, does not adequately address the issue of insulin resistance. Therefore, it is necessary to search for new agents with better efficacy and minimal side effects [8]. Since ancient times, herbs and plants have been used as medicines for many diseases, they are still considered as the basis of a system of traditional medicine in different cultures [9]. Among these medicinal plants is *Portulaca oleracea* which is a traditional vegetable is used by indigenous and tribal peoples in many countries. It is known to contain many biologically active compounds and is also reported as a source of many nutritional supplements [10]. On the other hand, *Aquilaria malaccensis* is a species of tropical plants of the family Thymelaeaceae [11]. It is one of the main sources of agar wood, which provides clues about their pharmacological properties. Indeed, agar wood contains several bioactive compounds that now elegantly support their use in traditional medicine [12]. Thus, the aim of this study is to evaluate the modulatory effect of the methanol extracts of *Portulaca oleracea* leaves and the trunk bark of *Aquilaria malaccensis* against high fructose and high fat diet induced insulin resistance metabolic disturbance and lipid peroxidation in rats.

Materials and Methods

Drugs and chemicals

Metformin was supplied in the form of tablets (Metformine Zentiva tablets, SAIDAL Group, Algiers, Algeria) and is given as a suspension in distilled water. Fructose was supplied as powder (Biomax, Specialized Food Industry, Algiers, Algeria). All other chemicals used in this study are of fine analytical grade.

Plant material

The plants used in this study are the bark trunk of *Aquilaria malaccensis* (*A. malaccensis*) which were purchased from the local market and

the leaves of *Portulaca oleracea* (*P. oleracea*) were harvested in the region of El-Oued “Guemar” in September 2016. The identity of plant was confirmed by a botanist at the herbarium in the Department of biology, the University of El Oued. The bark of *A. malaccensis* and leaves of *P. oleracea* were cleaned, dried in shade, powdered and then stored in air tight container until the beginning of the experiment.

Preparation of methanol extracts

The crude samples (each 3.75 g) were extracted by shaking with 25 ml of aqueous methanol (70:30) at 25 ° C for 48 h and filtered through filter paper. The residues were re-extracted with an additional 18.75 ml of aqueous methanol, as described above, for 3 hours. After extraction, the solvents were removed under low temperature (40 ° C) using a rotary evaporator.

Chemical characterization

Phytochemical Screening

Phytochemical tests were performed on extracts prepared from the plant by qualitative characterization techniques using standard screening test and phytochemical procedures.

Estimation of Total Phenol

The polyphenols were determined by the Folin-Ciocalteu method. This method, initially described by Slinkard and Singleton [13], makes it possible to know the total polyphenolic content of a given sample. The sample of the methanol extract of *A. malaccensis* or *P. oleracea* (0.5 ml) and 2 ml of sodium carbonate (75 g/l) were added to 2.5 ml of 10% (v/v) Folin- Ciocalteu with gallic acid as standard. After 30 min of reaction at room temperature, the absorbance was measured at 765 nm. The tests were carried out three times in order to ensure the reproducibility of the results. The total phenolic content was expressed in mg equivalent of gallic acid per gram of sample.

Estimation of Total Flavonoids

Determination of the total flavonoid content of the methanol extract of *A. malaccensis* and *P. oleracea* was carried out by the method described by Lin and Tang [14]. 0.5 ml of a 2% AlCl_3 ethanol solution was added to 0.5 ml of sample or standard. After 1 hour at room temperature, the absorbance was measured at 420 nm. Quercetin was used as a standard for plotting the calibration curve. The tests were carried out three times in order to ensure the reproducibility of the results. The results were expressed in milligram equivalent to Quercetin per gram of sample.

In-vivo study

Animals and treatment

Adult female albino rats (aged between 8–10 weeks), weighing 200–270 g, were taken from the animal house of Pasteur institute, Algeria. They were placed in six groups of five rats each and kept in animal house of Molecular and cellular biology Department, University of El Oued, Algeria. Animals were adapted for two weeks under the same laboratory conditions with a relative humidity 64.5% and room temperature of $25 \pm 2^\circ\text{C}$. After acclimation period, the rats were fed with either a high fructose diet, which is composed of 60% fructose (substituted for carbohydrates in the standard laboratory diet) and a high fat diet (60% kcal fat, 20% kcal carbohydrates, 20% kcal protein) (HFFD), or a normal chow diet (10% kcal fat, 70% kcal carbohydrates, 20% kcal protein) for 70 days. Mice were kept on a photoperiod (12 hr light/12 hr dark) and were fed ad libitum. After 60 days of feeding, the HFFD fed rats showed obvious phenotypes of insulin resistance (IR) compared to the normal diet control group. We then randomly divided them into six groups each containing five rats.

Group 1 (control group): animals were given normal diet served as control.

Group 2 (IR): insulin resistance rats were given HFFD diet.

Group 3 (IR+Po): Insulin resistance rats were given normal diet plus methanol extracts

of *P. oleracea* ($400 \text{ mg kg}^{-1} \text{ d}^{-1}$) administered orally.

Group 4 (IR+Am): Insulin resistance rats were given HFFD diet plus methanol extracts of *A. malaccensis* ($200 \text{ mg. kg}^{-1} \text{ .d}^{-1}$) administered orally.

Group 5 (IR+Po+Am): Insulin resistance rats were given HFFD diet plus both methanol extracts of *P. oleracea* and *A. malaccensis* administered orally.

Group 6 (IR+Met): Insulin resistance rats were given HFFD diet plus Metformine ($300 \text{ mg.kg}^{-1} \text{ .d}^{-1}$) administered orally.

Animals were maintained in the appropriate experimental treatments for 30 days. Body weight was recorded regularly. The experimental procedures were carried out according to the National Institute of Health Guide-lines for Animal Care and approved by the Ethics Committee of our Institution.

Blood collection and preparation of tissue samples

At the end of treatment, rats were fasted for 16 hours, anaesthetized with chloroform by inhalation, then rats were decapitated and blood samples were transferred into ice cold centrifuge tubes. The serum was prepared by centrifugation, for 10 min at 3000 revolutions/min and utilized for triglyceride, total cholesterol, HDL, urea, protein, creatinine concentrations and GOT, GPT, and ALP activities assays. The blood glucose was measured by glucometer. Absolute liver and kidney weight was determined while liver, kidney, and pancreas were rapidly excised, weighed and stored at -20°C for lipid peroxidation analysis.

Measurement of biochemical parameters

The activities of glutamate-oxaloacetate transaminase (GOT), glutamate pyruvate transaminase (GPT), alkaline phosphatase (ALP) were determined using commercial kits from Spinreact (Girona, Spain), triglyceride (TG), total cholesterol (TC), high density lipoprotein (HDL), total proteins, urea, and

creatinine concentrations were also measured using commercial kits obtained from Spinreact (Girona, Spain).

Lipid peroxidation measurement

Preparation of homogenates

1g of liver, kidney or pancreas was homogenized in 9 ml of buffer solution (phosphate buffer saline, pH=7.4). Homogenates were centrifuged at 9000xg for 15 min at 4°C, and the obtained supernatant was used for the determination of MDA parameter.

Estimation of Malondialdehyde (MDA) levels

Lipid peroxidation process was determined in supernatant of homogenate liver, kidney and pancreas tissues by the thiobarbituric acid (TBA) method which estimates the malondialdehyde formation (MDA) according to Sastre et al. (2000) [15]. Absorbance of TBA-MDA complex was determined at 530 nm and the level of hepatic MDA was expressed as $\mu\text{mol}/\text{mg}$ protein.

Statistical Analysis

The present data was reported as Mean \pm SEM. The significance of differences was calculated by using 1-way analysis of variance followed

by the Student t-test to compare means among the groups. Differences were considered statistically significant at $p < 0.05$.

Results

Phytochemical screening, Phenolic and Flavonoid Compounds

The results of phytochemical tests of various extracts which are presented in table 1 clearly show that the extracts of *P. oleracea* and *A. malaccensis* are rich in secondary metabolites including flavonoids tannins and saponins. From the results of quantitative analysis shown in Table 1, it was noted that the content of phenolic compound in the methanol extract of *P. oleracea* and *A. malaccensis* was very important which has 6.22 mg and 2.60 mg GAE per g of dry extract of each plant respectively. Similarly, Table 1 shows that the flavonoid content in *A. malaccensis* and *P. oleracea* extract is important, which has 0.255 and 0.528 mg QE per g of the dry extract of each plant, respectively.

Initial body weight, body weight gain and relative weight of liver and kidney

Our results (Fig 1) show that the induction of insulin resistance causes a significant increase ($p < 0.01$) of weight gain in rats compared to the control group. On the other hand, a significant decrease in weight gain is noticed in IR +Po

Table 1: Qualitative and quantitative analysis of phytochemical composition of methanol extract of *P. oleracea* and *A. malaccensis* (+ presence)

	Compounds	<i>P. oleracea</i>	<i>A. malaccensis</i>
Qualitative Analysis	Flavonoids	+	+
	Tannins	+	+
	Alkaloids	+	+
	Saponines	+	+
	Glycosides	+	+
Quantitative Analysis	Total phenolic (mg GAE/g extract)	6.226 \pm 0.189	2.609 \pm 0.094
	Flavonoids (mg QE/g extract)	0.255 \pm 0.011	0.528 \pm 0.007

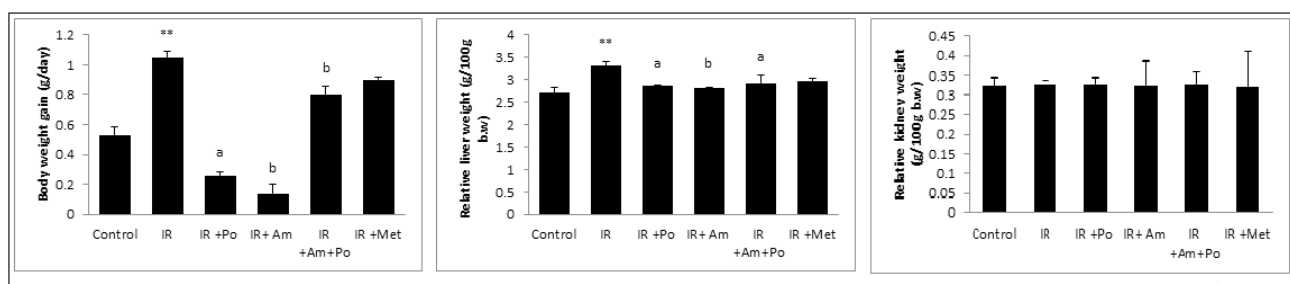


Figure 1: Mean body weight gain and relative liver and kidney weight of control and experimental rats. ** $p < 0.01$: significantly different from control group. ^a $p < 0.05$, ^b $p < 0.01$: significantly different from IR group.

($p < 0.05$), IR+ Am ($p < 0.001$), IR +Am+ Po ($p < 0.01$) and IR +Met ($p < 0.01$) groups compared to the IR group (Table 3). The results obtained show a significant increase in the relative liver weight ($p < 0.01$) in the IR group compared to the control group, but no change in the relative kidney weight. Treatment with *P. oleracea* and *A. malaccensis* extracts or both completely improves this anomaly compared to the IR group.

Blood biochemical values

As seen from Table 2, blood glucose level and serum lipid concentration was significantly altered which increased the level of glucose ($p < 0.01$), cholesterol, triglycerides ($p < 0.001$), low density lipoprotein (LDL) ($p < 0.01$), very low density lipoprotein (VLDL) ($p < 0.001$) liver

triglycerides ($p < 0.01$), liver cholesterol ($p < 0.001$), adipocytes triglycerides ($p < 0.001$) and Adipocytes cholesterol ($p < 0.05$) at the end of the treatment period in IR animals as compared to normal animals. Moreover, the results obtained show that there is a significant improvement in the blood glucose level, serum and tissues triglyceride, cholesterol, VLDL and LDL concentrations in the rats treated with extract of *P. oleracea* (Po), *A. malaccensis* (Am), Po + Am and Metformin (Met) compared to IR group while only treatment significantly increases the HDL level compared to the IR group.

Liver and renal function markers

As indicated in Table 3, insulin resistance induced a renal dysfunction with a significant ($p < 0.05$) increase in urea and creatinine

Table 2: Mean blood glucose and lipid profile in serum and tissues of control and experimental rats.

Groups	Control	IR	IR +Po	IR+ Am	IR +Am+ Po	IR +Met
Blood Glucose (mg/dl)	101±2	182±4***	109±9.1 ^b	109±8.2 ^b	115±1.3* ^b	117±1.2** ^b
Serum TG (mg/dl)	83.5±6.4	177.2±4.5**	104±6.49 ^c	64.25±8.28 ^c	73.50±5.42 ^c	71.50±5.32 ^c
Serum TC (mg/dl)	54.2±4.3	83.5±2.2**	51.7±2.2 ^b	52.0±1.2 ^b	54.7±1.9 ^b	53.0±5.3 ^b
Serum HDL (mg/dl)	17.6±0.8	15.1±1*	17.0±0.2 ^b	17.4±0.5 ^b	16.4±0.9*	16.7±0.7
Serum LDL (mg/dl)	16.2±1.6	29.4±1.5***	15.6±2.8 ^c	19.2±2.1 ^c	19.5±0.03.5 ^c	20.4±2.2 ^c
Serum VLDL (mg/dl)	16.7±1.3	35.44±0.9**	20.8±1.29 ^c	12.85±1.65 ^c	14.7±1.08 ^c	14.3±1.06 ^c
Liver TG (mg/g tissue)	5.13±0.27	9.18±0.27**	6.03±0.36	5.13±0.09 ^c	5.76±0.27 ^b	6.21±0.27 ^b
Liver CHL (mg/g tissue)	5.22±0.09	7.74±0.26***	5.76±0.18 ^a	4.95±0.25 ^b	5.85±0.17 ^b	6.39±0.18 ^a
Adipocytes TG (mg/g tissue)	10±0.8	50.8±2.9***	38.6±3.5*** ^a	35.46±1.9*** ^b	37.3±1.2*** ^a	37.5±0.6*** ^a
Adipocytes CHL (mg/g tissue)	1.62±0.09	2.88±0.16*	2.16±0.054 ^a	1.80±0.09 ^b	2.43±0.18*	2.25±0.09*

Data is expressed as Mean ± SEM, (n=5 animals/group).

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$: significantly different from Normal group.

^a $p < 0.05$, ^b $p < 0.01$, ^c $p < 0.001$: significantly different from IR group

concentration and a significant decrease ($p < 0, 01$) of total protein concentration in rats of IR group compared to controls. On the other hand, treatment with the methanol extract of *P. oleracea* (Po), *A. malaccensis* (Am) or Po+Am corrects these disturbances compared to the untreated IR rats. For liver function markers, the results showed a significant ($p < 0.05$) increase in transaminases activities (GOT and GPT) and alkaline phosphatase in IR group compared to control. In contrast, a significant decrease ($p < 0.05$) of GOT and GPT activities was reported under the effect of treatment with extract of *P. oleracea* (Po) or *A. malaccensis* (Am) and a decrease in ALP and GOT activities in the group treated with Po + Am compared to untreated IR rats. Regarding treatment with metformin, results didn't notice any significant improvement in liver function in comparison with the IR group.

Lipid peroxidation marker

The obtained results (Fig. 2) showed a significant increase ($p < 0.05$) of lipid peroxidation in the liver, kidneys and pancreas in

insulin resistance (IR) group. While treatment with *P. oleracea* (Po), *A. malaccensis* (Am) or Po + Aq leads to a significant reduction ($p < 0.05$) in hepatic, renal and pancreatic MDA levels compared to the IR group. Finally, there was only a significant decrease in pancreatic MDA concentration in the metformin-treated rats compared to the IR group.

Discussion

The results of the phytochemical analysis revealed that the methanol extract of dry leaves of *Portulaca oleracea* and the trunk bark of *Aquilaria malaccensis* contains several bioactive compounds, including polyphenols, saponins, tannins, alkaloids, and flavonoids. Dietary phytochemicals can act on one or more molecular targets that relieve multiple pathological processes, including oxidative damage, epigenetic alterations, chronic inflammation, active stimulators, inhibitors and growth terminators and prevention of various diseases associated with oxidative stress [16]. In our study, results showed

Table 3: Mean serum kidney function markers and enzymes activities in control and experimental rats.

Groups	Control	IR	IR +Po	IR+ Am	IR +Am+Po	IR +Met
Serum creatinine (mg/l)	8.3±0.15	10.40±0.47*	8.42±0.35 ^a	8.15±0.22 ^b	7.950±0.290 ^a	7.900±0.10 ^a
Serum urea (g/l)	0.58±0.03	0.87±0.04*	0.66±0.02 ^a	0.62±0.03 ^b	0.715±0.04 ^a	0.64±0.05 ^a
Serum protein (mg/l)	46.21±2.18	32.83±0.51**	38.78±1.11 ^b	39.20±1.46 ^b	34.02±1.06*	36.31±0.52 ^a
Serum ALP (U/l)	38.30±1.30	43.86±1.49*	38.13±2.36**	37.74±1.84	38.96±1.08	39.32±1.57
Serum GOT (U/l)	132.7±1.32	143.89±1.21*	134.18±2.71 ^a	131.96±1.24 ^a	133.51±3.52 ^a	130.34±4.91 ^a
Serum GPT (U/l)	36.42±1.4	53.12±0.9**	33.06±2.76 ^b	34.63±1.44 ^b	31.16±3.05 ^b	33.30±6.65

Data is expressed as Mean ± SEM, (n=5 animals/group).

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$: significantly different from Normal group.

^a $p < 0.05$, ^b $p < 0.01$, ^c $p < 0.001$: significantly different from IR group.

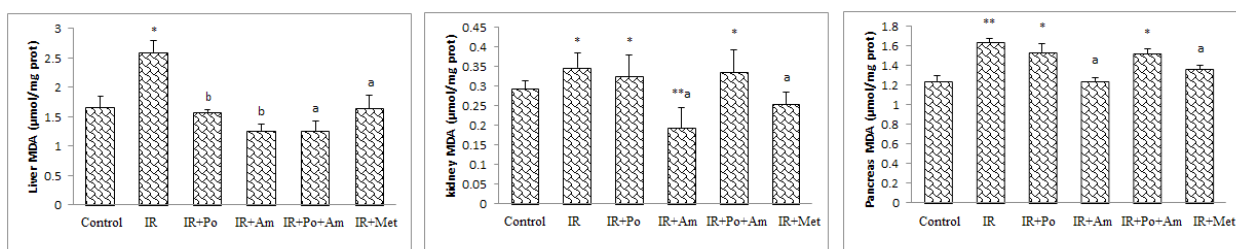


Figure 2: Mean MDA level in liver, kidney and pancreas tissues of control and experimental rats. * $p < 0.05$, ** $p < 0.01$: significantly different from control group. ^a $p < 0.05$, ^b $p < 0.01$: significantly different from IR group.

that in rats receiving a high fat diet with high fructose causes a significant increase in weight gain and relative liver and kidney weight resulting in an obese phenotype. More consumption of high energy content nutriment such as fructose and HFD leads to rise in the fat mass and fat cell expansion (hypertrophy) without changing food intake, producing the specific pathology of obesity [17]. Also high proportion of lipids in food can increase palatability and cause hyperphagia of animals leading to rapid weight gain [18]. Treatment of insulin-resistant rats with the methanol extract of *P. oleracea* and/ *A. malaccensis* induces a decrease in body weight gain. The anti-obesity properties of plants can be exerted according to different modes of action: by direct effect on food intake by suppressing appetite and inducing the feeling of satiety, a reduction of lipid absorption, a reduction of energy consumption, increased energy expenditure, decreased pre-adipocyte differentiation and proliferation, decreased energy intake from the gastrointestinal tract [19]. Our results show a disruption of lipid and carbohydrate metabolism under the effect of HFFD regime. The Cafeteria diet also leads to excessive development of adipose tissue which could be due to a decrease in the ability to oxidize dietary lipids and enlargement of adipocytes (hypertrophy). In addition, fat accumulation is regulated by the lipolysis cycle, lipogenesis [20]. This explains the high level of triglycerides and cholesterol in adipose tissue in diet-fed rats (HG + F) compared with standard diet rats, this is consistent with the BOCARSLY et al. (2010) study which shows high fructose content causes characteristics of obesity in rats, increased body weight and body fat [21]. In rodents, a high-fructose diet leads to the development of obesity insulin resistance, suggesting that fructose is the main mediator of glucose intolerance and insulin resistance [22]. Fructose has a less inducing mechanism of satiety than glucose / sucrose, and will also decrease the sensitivity of the liver and peripheral tissues to insulin which is explained as hyperglycemia [23]. Treatment with *A. malaccensis* induces a reduction in hyperglycemia and dyslipidemia, the anti-hyperglycemic agent and glucose uptake enhancement activities of methanol

extracts of *A. malaccensis* are similar to those of insulin [24]. In addition, *A. malaccensis* is rich in flavonoids which is able to reduce the increase in blood glucose levels and increase glucose uptake in rat muscle more effectively than insulin [25]. Our results also showed that treatment with *P. oleracea* exerts a hypoglycemic, hypolipidemic effect and significantly reduces weight gain. The anti-hyperglycemic activity of *P. oleracea* can be attributed to the presence of polyphenols reported as a major role in the reduction of diabetes that helps regulate plasma glucose levels and hepatic glucose metabolism which could inhibit digestive enzymes such as salivary amylase, intestinal sucrose and α -glucosidase. This reduced the action of digestibility and promoted the regeneration of pancreatic β cells and increase the muscle glucose transporter [26]. The results show hepatic and renal dysfunction and increase in lipid peroxidation induced by fructose diet. Liver tissue lesions due to hyperlipidemia impair their transport function and membrane permeability, leading to enzyme leakage from cells, therefore, marked release of GOT and GPT in the circulation indicates severe damage to hepatic tissue membranes [27]. Indeed, elevation of creatinine and urea and decrease in protein may explain the diabetic nephropathy which is the main determinant of morbidity and mortality in patients with diabetes. Chronic hyperglycemia is a major initiator of disruption of renal function [28]. High fructose and HFD has been identified to increase the tissues mitochondrial reactive oxygen species (ROS) production. Excessive ROS production under insulin resistance/hyperglycemic conditions attacks local cell organelles, including membrane lipids, resulting in lipid peroxidation [29]. In contrast, treatment with *P. oleracea* and/ or *A. malaccensis* shows a significant decrease in ASAT, ALAT and PAL activities and module urea and creatinine concentrations compared to insulin-resistance rats. This protective action may be due to the improvement of fat accumulation in the liver and a rapid restoration of insulin sensitivity in the liver, at least at an early stage of hepatic insulin resistance [30]. In fact, the hypoglycaemic effects of two plants may be associated with nephroprotection, flavonoids

having a protective effect on renal dysfunction in rats which were fed a high fructose diet, by modulating the pathological pathways induced insulin resistance.

Conclusion

In conclusion, this study clearly shows that the Methanol extract of bark *A. malaccensis* and leaves of *P. oleracea* possess the ability to control the biochemical disruption associated with insulin resistance, antioxidant action and protective activity on liver, kidney and pancreatic cells, which in turn will improve the energy metabolism.

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Conflict of interest

The authors declare no conflict of interest.

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