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Anti-diabetic and lipid-lowering effects of drimane sesquiterpenoids isolated from *Zygogynum pancheri*

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Abbreviations:

T2D, type 2 diabetes; STZ, streptozotocine; DMSO, dimethyl sulfoxide; FBG, Fasting Blood Glucose; TGs, triglycerides; T-Ch, total cholesterol; HDL-c, high-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase,

ABSTRACT

Background: Recently, it has been shown that drimane-type sesquiterpenoids isolated from *Zygogynum pancheri*, a species native to New Caledonia, possessed significant α -amylase inhibitory activities.

Purpose: To further explore their antidiabetic potential, we investigated the effect of 1 β -*O*-(*E*-cinnamoyl)-6 α -hydroxy-9*epi*-polygodial (D) and 1 β -*E*-*O*-*p*-methoxycinnamoyl-bemadienolide (L), two of the most active compounds of the series, on diabetic model rats.

Methods: Compounds D and L (2 mg kg/day) were daily and orally administered for 30 days to streptozotocin (STZ) (150 mg/kg) induced male diabetic Wistar rats. Animals were allocated into five groups of six rats.

Results: Comparatively to diabetic rats, treatments with D and L compounds were able to significantly ($P < 0.05$) decrease Fasting Blood Glucose (FBG) (70.15%, 71.02%), serum total cholesterol (46.27% and 39.38%), triglycerides (56.60% and 58.15%), creatinine (37.31% and 36.49%) and uric acid levels (67.76% and 69.68%), respectively. Compounds D and L also restored the altered plasma enzyme (aspartate aminotransferase, AST (47.83% and 43.20%), alanine aminotransferase, ALT (49.76% and 48.35%, alkaline phosphatase, ALP (72.78% and 73.21%)) and lactate dehydrogenase, LDH (47.95% and 53.93%) levels to near normal, respectively. Administration of Glymepiride, significantly ($p < 0.05$) reduced FBG (73.94%) in STZ induced diabetic rats. Additionally, the compounds D and L exhibited inhibitory effects *in vivo* on lipase activity of diabetic rats (54.83% and 52.25%), respectively.

Conclusion: The outcomes of this study suggested that these two drimanes could be considered as efficient hypoglycemic, hypolipidemic and antiobesity agents for diabetes management and its complications.

Keywords: Winteraceae, *Zygodium pancheri* subsp. *arrhantum*, streptozotocin, hypoglycemia, hypolipidemia.

Introduction

Diabetes mellitus is a major and growing public health problem throughout the world, with an estimated worldwide prevalence in 2030 to 578 million and to 700 million in 2045 (Saeedi et al., 2019). It is a heterogeneous disorder with varying prevalence among different ethnic groups and is reported to constitute the 16th leading cause of global mortality (Danaei et al., 2011), (Sundaram et al., 2012). It is characterized by abnormalities in carbohydrate, lipid and lipoprotein metabolisms, which not only lead to hyperglycemia but also cause many complications, such hyperinsulinemia, hyperlipidemia, atherosclerosis and hypertension (Ozkan et al., 2016).

There are two main types of diabetes characterized by insulin defects: type 1 diabetes (T1D) defined by insulin deficiency and type 2 diabetes (T2D) characterized by insulin resistance (Verma and Hussain, 2017). The conventional pharmacological treatments for diabetes have a number of limitations, such as adverse effects and high rates of secondary failure. However, medicinal herbs are expected to have a similar degree of efficacy without the troublesome side effects associated with conventional synthetic drug treatments. This explains the growing interest in herbal remedies for diabetes treatment (Kim et al., 2006).

Previously, it has been reported that drimane sesquiterpenoids were the main constituents present in the bark and the leaves of various New Caledonian species of the genus *Zygodium*, one of the two genera of the family Winteraceae occurring on mainland Australia and offshore islands (Allouche et al., 2009, Keskes et al., 2014, Fomekong Fotsop et al., 2008). Many of them, which have the particularity to bear a cinnamoyl ester moiety in position 1, have been isolated in large quantities and as such are considered to be good chemotaxonomic markers of this genus (Allouche et al., 2009). The *Zygodium* genus consists of about 41 species, of which 18 species are endemic to New Caledonia (White and Vink, 1993).

These drimane sesquiterpenoids are known to possess antifungal, antibacterial, molluscicidal, antifeedant, piscicidal, phytotoxic, cytotoxic (Jansen and Groot, 2004, Allouche et al., 2009) and glucosidase inhibiting properties (Harinantenaina et al., 2007).

Recently, Keskes et al. (2014) showed that drimane-type sesquiterpenoids bearing a cinnamoyl ester group isolated from a *Zygodium pancheri* subsp. *arrhantum* EtOAc bark extract possessed significant α -amylase inhibitory activities ((Keskes et al., 2014). Among the compounds isolated, the drimanes 1 β -*E-O-p*-methoxycinnamoyl-bemadienolide, 1 β -*O-(E-cinnamoyl)-6* α -hydroxy-9-*epi-*

polygodial, 1 β -*O*-(*E*-cinnamoyl)-6 α -hydroxypolygodial, and 1 β -*O*-*E*-cinnamoylpolygodial exhibited highest α -amylase inhibitory activities, while cinnamolide, a structurally close analogue of 1 β -*E*-*O*-*p*-methoxycinnamoyl-bemadienolide but without the ester moiety, was found inactive. For this reason and given that several of the above-mentioned compounds have been isolated in large quantities we undertook an in-depth study of the antidiabetic properties of 1 β -*O*-(*E*-cinnamoyl)-6 α -hydroxy-9-*epi*-polygodial (denoted D) and *E*-*O*-*p*-methoxycinnamoyl-bemadienolide (denoted L). Moreover, it is interesting to note that drimane D can spontaneously be rearranged under acidic conditions to give the lactone L (Fomekong Fotsop et al., 2008).

Therefore, in order to compare the effect of the two drimanes on diabetes. Their antidiabetic effects, were evaluated and compared in streptozotocin induced diabetic rats.

Materials and methods

Reagents

1 β -*O*-(*E*-cinnamoyl)-6 α -hydroxy-9-*epi*-polygodial (D) and 1 β -*E*-*O*-*p*-methoxycinnamoyl-bemadienolide (L) (Figure 1) have been isolated from the bark t of *Zygodinium pancheri* subsp. *arrhantum* as previously described (Allouche et al., 2009).

Determination of lipase activity in vitro

The method was modified from the assay reported by (Nakai et al., 2005) who used 4-ethylumbelliferyl oleate (4-MU oleate) (Biolabo, France) as a substrate to measure the pancreatic lipase inhibitory activity of plant extracts. The assay consisted to mix the pancreatic lipase (Biolabo, France) solution with 4-MU oleate solution. The plate was immediately placed in the 37°C preheating FL \times 800 micro plate fluorescence reader to measure the amount of 4-methylumbelliferone released by lipase every minute for 30min at an excitation wavelength of 360 nm and an emission wavelength of 455 nm. The lipase inhibitory activity was determined by measuring the effect on the enzyme reaction rate after adding extracts, compared with the positive control: Glymepiride (Amarel 3 mg, Pharmacy of the medical herbalist Mohamed Dammak, Sfax-Tunisia) (Belhadj et al., 2018). The inhibition percentage (IP) is expressed according the equation 1.

$$IP = \frac{\text{Absorbance}_{\text{control}} - \text{Absorbance}_{\text{test}}}{\text{Absorbance}_{\text{control}}} * 100 \quad (1)$$

Routine breeding of animals

Adult male Wistar rats used in this study, were provided by the Tunisian Central Pharmacy (SYPHAT) and were selected according to their body weight (bw = 180–200 g). They were fed with a pellet diet (SICO, Sfax, Tunisia) and water was allowed ad libitum under strict hygienic conditions. Before initiation of experiment, the rats were maintained in the quarantine for a period of 7 days under standard abiotic defined by a temperature ($22 \pm 2^\circ\text{C}$), a relative humidity (45–55%) and a 12/12 h dark/light cycle. The Tunisian Ethical Committee for the care and use of laboratory animals approved the handling of the animals.

Induction of diabetes in experimental animals

Rats were injected intraperitoneally with a freshly prepared solution of STZ at a dose of 40 mg/kg bw for 15 days (Arokiyaraj et al., 2011).

At the end of the induction period, rats displaying glycosuria and hyperglycemia ($> 2 \text{ g/l}$) were chosen for the experiments.

Experimental procedure

Five groups of rats, six in each received the following treatment schedule.

Group I: Normal rats (Ctr);

Group II: STZ-induced-diabetic rats (Diab.);

Group III: STZ-induced-diabetic rats treated with compound D which was administrated at 2 mg/kg bw (Diab+D);

Group IV: STZ-induced-diabetic rats treated with compound L at 2 mg/kg bw (Diab+L);

Group V: STZ-induced-diabetic rats treated with Glimepiride 3 mg/kg bw (Diab+Gly).

The two compounds were dissolved in drinking water and dimethyl sulfoxide (DMSO) at a concentration of 3%. After 1 month of treatment, the animals were sacrificed, and the blood was collected. Liver, kidney and pancreas were rapidly removed and cleaned of fat. All these samples were stored at -80°C until used.

Biochemical variables and blood glucose determination

Fasting Blood Glucose (FBG) was assayed by glucose oxidase, using a commercial kit (Biomaghreb, Tunisia).

The analyses of plasma lipase and plasma triglycerides (TGs), total cholesterol (T-Ch), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c) levels, were measured using the corresponding commercial kits (Biolabo, France).

Plasma levels of creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), creatinine and uric acid were measured in frozen aliquots of plasma by standardized enzymatic procedures using commercial kits (Biolabo, France).

Statistical Analysis

Statistical analysis was performed using the statistical Package for Statistica. Data are presented as means \pm Standard Error of the Mean (SEM). Statistical significance was assessed using one-way analysis of variance (ANOVA) followed by the Fisher test (at $P < 0.05$ the differences were considered statistically significant).

Results

Alpha-amylase activity in plasma and FBG

The results revealed that diabetes induced a significant ($P < 0.001$) increase in the α -amylase activity in the plasma by 42.19% which leads to an increase rate by 73.54 % of the FBG. In drimanes treated diabetic rats, the activity of this enzyme underwent a considerable improvement. Indeed, as compared to Diab group, the compounds D, L and glibenclamide succeeded to reduce by 44.57%, 44.93% and 42.20% this enzyme activity, respectively.

Hence, this potential inhibitory effect of the compounds D, L and Glibenclamide was confirmed by a strong significant ($P < 0.001$) reduction of FBG by 70.15%, 71.02% and 73.94%, respectively (Fig. 2B).

The histology of the pancreas in diabetic rats (Fig. 3B) showed an atrophication of Langerhans islets and a reduction in the number of cells by comparison with Langerhans islets in control rats (Fig. 3A). In contrast, treatment of diabetic rats with drimanes and glibenclamide (Fig. 3C, Fig. 3D and Fig. 3E) has shown potential protection of pancreatic tissues with regeneration of Langerhans islet cells.

Effect of compounds D and L on pancreatic lipase levels

Figure 4 evidenced that compared to the control rats, there was a significant ($P < 0.05$) rise in the activity of pancreatic lipase in plasma of untreated diabetic rats by 52.68 %. However, the administration of compound D and compound L induced a considerable reduction in plasma lipase

activity by 54.83% and 52.25%, respectively. As expected, a significant ($P < 0.001$) improvement (55.70%) in the drug treated group (Diab+Gly) was registered compared to untreated one (Diab).

Effect of compounds D and L on lipid profiles

In diabetic rats, significant ($P < 0.001$) increases of plasmatic T-Ch (Fig 5A) and TGs (Fig 5B) levels (34.40% and 60.19%, respectively) as well as a significant decrease of plasmatic HDL-c level (20.22 %, Fig 5C) were observed as compared to Ctr group.

However, the administration of compound D (Diab+D) to diabetic rats significantly ($P < 0.001$) reduced T-Ch (Fig. 5A) and TGs (Fig. 5A) levels in plasma (37.63% and 50%, respectively). This reduction was even better after the administration of the compound L (43.31% Fig. 5A and 53.79% Fig. 5B, respectively) as compared to Diab groups.

Even though the compound D (Diab+D) succeeded to significantly ($P < 0.05$) increase plasmatic HDL-c, the glymeperide and compound L did not exhibit significant differences with diabetic rats.

Effect of compounds D and L on liver parameters

Data in Table 1 showed an increase of the liver digestive parameters in the Diab group. Comparatively to Ctr group, AST, ALT and ALP activities increased by 42.41%, 80.32% and 75.80% in the Diab group, respectively. The appearance of fat cells (Fig.6B) in liver tissue confirmed the installation of the metabolic disorder. However, treated rats with compound D (Diab+D) and L (Diab+L), a notable protective effect was observed in hepatic function and tissue integrity. In fact, their administration to diabetic rats significantly decreased AST and ALT and ALP rates (57.27%, 51.42%, 65.85% respectively with the compound D and 47.66%, 45.08%, 53.78% respectively with the compound L).

Histological findings (Fig. 6C and 6D) confirmed the positive effects of these molecules. The cinnamates administration to diabetic rats reduced the appearance of fat cells in the liver (Fig. 6B) and was as efficient as glymeperide (Fig. 6E).

Effect of compounds D and L on atherogenic index (LDH)

This current study indicated a significant ($P < 0.001$) elevated levels of LDH activities (48.14%), in plasma of Diab group as compared to Ctr group. This higher level of atherogenic index observed in Diab group was significantly reverted towards normal levels after treatment with naturel resources (Diab+D: $885.21\text{UI/l} \pm 6.71$ and Diab+L: $786.24\text{UI/l} \pm 63.22$) and Glimeperide (Diab+Gly: $1013.67\text{UI/l} \pm 96.55$) (Table 1).

Effect of compounds D and L on kidney

Results in table 1 showed that hyperglycemia (Diab group) induced kidney toxicity as indicated by a significant increase of creatinine and uric acid rates in plasma by 38.44% and 69.03%, respectively, when compared to Ctr group. In addition, kidney sections in Diab group showed a glomerular condensation (Fig.6B). Interestingly, the administration of Compound D (Diab+D), L (Diab+L) and Glimperide to diabetic rats reverted towards normal levels the above biochemical indices, improved Bowman's capsule thickness and cellular contiguity in glomerulus (Fig. 7).

Discussion

The purpose of this study was to evaluate for the first time the antihyperglycemic, hypolipidemic and anti-obesity effects of Sesquiterpene dialdehyde cinnamates *in vitro* and *in vivo* and to compare these effects between two particular compounds 1 β -*O*-(*E*-cinnamoyl)-6 α -hydroxy-9*epi*-polygodial (compound D) and 1 β -*E*-*O*-*p*-methoxycinnamoyl-bemadienolide (compound L).

Our results showed a protective effect of these natural substances against streptozotocin-induced diabetes in Wister rats through the modulation of α -amylase, lipase, glycemia, lipid profile, liver parameters and atherogenic index. In fact, the effect of the Sesquiterpene dialdehyde (D) cinnamates was comparable to that of lactone (L).

In our experiments, the STZ-induced diabetic model have been used for many reasons, including pancreatic swelling, causing degeneration in Langerhans islet beta cells and resulting in hyperglycemia and hyperlipidemia (Akbarzadeh et al., 2007). The diabetic state caused by STZ is due to its generation of nitric oxide and free radicals that disrupt the mitochondrial function of beta cells (Rakieten et al., 1963).

Alpha-amylase is a key enzyme in the treatment of diabetes. It breaks down the polysaccharides' complex and consequently it limits the glucose uptake by inhibiting the intestinal enzyme, α -glucosidase (Saito et al., 1998).

Both drimanes similarly inhibited α -amylase resulting in decreased FBG in STZ-induced diabetic rats. Our findings confirm those of Keskes et al. (2014) who reported the inhibitory effect on α -amylase activity *in vitro* of these two compounds.

Indeed, several researchers (Qin et al., 2003, Khan et al., 2003) have proved that the presence of cinnamoyl acid function in compound D and L was responsible for the efficient reduction of glycemia.

The cinnamoyl acid function might also inhibit hepatic glucogenesis by inducing glucose uptake or stimulating insulin secretion by the remaining pancreatic beta cells and generation of other cells as confirmed by the pancreas sections.

More, the anti-hyperglycemic cinnamaldehyde effect was significantly comparable to glimepiride. To stimulate insulin secretion by pancreatic β -cells, this standard hypoglycemic drug is a conventional medicine to treat diabetes since many years. The similarity between blood glucose levels obtained after treatments by the drug and the two compounds, strongly suggest that the tested drimanes (D and L) in this study would act through the same mechanism as glimepiride, which is potentiation of insulin secretion and action by the remaining β cells in the Langerhans islets.

Pancreatic lipase is a key enzyme in the treatment of obesity, considered among the most important targets for the development of anti-obesity drugs. As a primordial lipolytic enzyme, pancreatic lipase is responsible for the hydrolysis of 50-70% of the total dietary fat in the intestinal tract (Ha et al., 2016).

Our results showed a good lipase activity by both drimanes extracted from *Zygogynum. pancheri in vivo*. There are no research works that explain the mechanism of inhibition of these drimanes on the pancreatic lipase activity.

An important outcome of our study is that the compound D and L boosted pancreatic lipase to break down dietary fat so that it is well absorbed in the intestine.

Dyslipidemia is one of the secondary complications of diabetes that accompanies long-term diabetes (Mooradian, 2009). This imbalance is characterized by an increase of T-Ch, TGs and LDL-c levels and a decrease of the good cholesterol (HDL-c) level (Arvind et al., 2002). In diabetes, these abnormal blood lipid levels have been reported to be the intimate consequence of the excessive action of the hormone-sensitive enzyme, the pancreatic lipase (Adedeji et al., 2007).

The insulin deficiency and consequently the mobilization of free fatty acids highly contribute to increase the lipid levels in diabetes (Schofield et al., 2016). Generally, in mammals, the pancreas, liver, kidney and adipose tissue are the key organs simultaneously concerned by the metabolic syndrome of diabetes.

The liver plays a very important role in the maintenance of a balanced glycemia through the regulation between glyneocogenesis (decreasing glycemia) and the glycogenolysis gluconeogenesis increasing glycemia), and in the post-absorption state (Sherwin, 1980).

In the current work, the carbohydrate metabolism disorder observed in STZ-induced diabetic rodents, lead to the increase of ALT, AST and LDH blood levels, creatinine and uric acid.

LDH, ALT and AST are enzymes mainly found in the cytosol and the cell membrane of liver cells. These are the markers often used to evaluate liver function and more specifically hepatotoxicity. Their high records reflected the liver dysfunction in Diab group. Similarly, Larcan et al. (1979) reported that liver tissue was necrotic in diabetic patients. The disruption of the hepatocyte membranes and the leakage of LDH and transaminases out of the cells to the blood circulation are the main reasons for their elevated plasmatic concentrations (Bouché et al., 2004). This clearly shows the hepatotoxicity as an evidenced action of hyperglycemia.

Oral administration of the natural compounds D and L and gylmepiride to the Diab group, has shown an improvement of the LDH and transaminases to normal levels. These latter allowed a clear disappearance of fat lipid droplets in the liver parenchyma with well- sharpened borders between contiguous hepatocytes.

The excessive excretion of urine called polyuria, the increase of creatinine and uric acid levels compared to healthy being observed during the assays, were among the expected complication symptoms of the stably installed diabetes.

As major excretory organs in diabetes, the kidneys were profoundly affected by hyperglycemia forcing them to an intensive filtration from the micro vessels, and a failure of the nephric tubules to reabsorb the glucose again.

The excess of glucose passes in the urine (glycosuria) thus proving an osmotic diuresis and consequently the polyuria (Andrianesis et al., 2016).

The creatinine content in the internal medium reflects a balance between the production of waste and elimination by the glomeruli filtration-(Andrianesis et al., 2016).

Treatment with compound D and L succeeded to reestablish normal rates of creatinine and uric acid translating the positive effect of these two molecules on the reuptake of glucose molecules in the proximal glomeruli tubules. This significant decrease was equal to the one noticed in Ctr and Diab+Gly groups.

The profits on excretion function brought by the tested drimanes were also confirmed by renal sections where they proved to be as efficient as gylmepiride and similar to control group.

Conclusion

The novelty of this study consisted in comparing the effects of the drimanes D and L isolated from *Zygogynum pancheri*: *O*-(*E*-cinnamoyl)-6 α -hydroxy-9*epi*-polygodial (D), a

compound that is quantitatively transformed into 1 β -*E-O-p*-methoxycinnamoyl-bemadienolide (L) in acidic medium.

Gathered the results of this work demonstrated that the compounds D and L revealed a protective effect against STZ-induced diabetes in Wistar rats.

Administered at 2 mg kg⁻¹ bw, these two molecules (dialdehyde D and lactone L) showed comparable effects and acted as antidiabetic and anti-obesity agents by catching the digestion of carbohydrates and lipids through the pancreatic α -amylase and pancreatic lipase inhibition, respectively, thus decreasing glycemia.

The tested molecules could modulate the liver parameters, renal biomarker concentrations and atherogenic index.

Both molecules were not toxic in diabetic rats. Indeed, the histological sections of pancreas, liver and kidney showed a normal-like protection of the tissue targeted organs thus reducing or avoiding their toxicities.

Corroborating results handled by this research, it was possible to stipulate that 1 β -*O-(E-cinnamoyl)-6 α -hydroxy-9 ϵ pi-polygodial* (D) and 1 β -*E-O-p*-methoxycinnamoyl-bemadienolide (L) represented bioactive supplements for oral use to treat diabetes and metabolic complications including obesity.

As it stands, this study is conclusive but the mechanism of actions of these two molecules is still unknown.

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