


Anti-diabetic role of quercetin and cinnamon on neurobehavioral alterations and biochemical parameters of induced diabetics rats



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Abstract We aim was to evaluate the protective effects of the antioxidants cinnamon and quercetin on neurobehavioral alterations and complications, besides biochemical parameters of induced-diabetics Wistar rats. Diabetes was induced by a single intraperitoneal injection of streptozotocin at a dose of (45 mg/kg). The administration of streptozotocin was considered acting on anxiety behaviors and biochemical parameters in adult Wistar rats. On the other hand, the protective role of antioxidants (cinnamon and quercetin) on streptozotocin-induced disorders was also evaluated. Behavioral tests in the open field (OF) revealed that diabetic animals exhibited an anxious behavior and an alteration in the locomotive and exploratory activities when compared to control. The administration of the cinnamon (2g/kg) and Quercetin (0.5g/kg) by gastric gavage reduces anxiety and decreases hyperglycemia-related harm. However, antioxidants cinnamon and quercetin administration significantly alleviated anxious and depressive behaviors.

Keywords: antioxidants, anxiety, diabetes

Introduction

Diabetes is a significant health problem whose frequency is increasing. It results in severe acute complications (hypoglycemia, hyperglycemia) or chronic ones (ophthalmic problems, nephropathy, neuropathy, and foot problems (Wens et al 2007). This pathology has been known for many years, and given its growing prevalence around the world, scientists have been working on different treatments attempting to reduce it (Deplech 2015).

To understand the pathophysiological mechanisms associated with the diabetic syndrome, it is possible to reproduce in animals a diabetic state simulating human diabetes by various experimental methods: chemical, surgical, or genetic (immunological) (Etuk and Muhammed 2010).

Streptozotocin, in high doses, destroys B cells; at low and repeated dose, it induces insulinitis followed by the destruction of B cells by a T cell-dependent immune mechanism (Grimaldi 2000). The peripheral neurological complications of diabetes are frequent, various, inaugural, or latent (Ghika et al 2003).

Stress has long been considered as an important factor in type 2 diabetes. However, it is only recently that researches have shown how stress can play a role in triggering diabetes and controlling blood sugar for people with diabetes (Surwit 2002).

Research is showing more and more the relationship between mental disorders and diabetes. People with serious mental disorders, particularly those with depressive symptoms or syndromes, and people with diabetes have reciprocal susceptibility and a high rate of conditions involving mental health (David et al 2013).

Nowadays, the therapeutic virtues of plants are showing renewed interest thanks to the improvement of extractive techniques and the progress of structural analysis methods for the discovery of new active principles (Saffidine 2015).

The polyphenols form an important group of natural substances that are widespread in the plant world (Urquiaga 2000; Saffidine 2015). Flavonoids are the main group of polyphenols, with more than 9000 different compounds and distributed in a general way (Hernández 2009; Saffidine 2015). They are amongst the most representative substances produced by plants through their secondary metabolism; these substances possess coloring, aromatic, medicinal, and cosmetological properties and confer on the plant's adaptive advantages. Many active ingredients are beneficial to humans and animals (Saffidine 2015); they are recognized primarily for their antioxidant action (Bruneton 1999).

In this context, we aim was to evaluate the protective effects of the antioxidants Cinnamon and Quercetin on

neurobehavioral alterations and complications, besides biochemical parameters of induced- diabetics Wistar rats.

Materials and Methods

Biological material

The basic biological material we have opted for is the white rat of the Wistar strain from the Pasteur Institute in Algiers. On arrival, these rats weighed on average 150 grams, and at the time of the experiment, they weighed on average 210 ± 20 grams. These animals were acclimated to the conditions of the animal house, at a temperature of 25 ± 2 °C, a hygrometry of 50%, and a natural photoperiod (spring). The food provided to the animals is made in the form of sticks consisting of corn, barley, milk, and vitamin supplements (GAE: Eastern Agricultural Group, Bejaia). As for drinking water, it is presented in bottles adapted to the cages. Food and water are provided *ad libitum*.

After a three-week adaptation period, we selected twenty-four weight-based rats (approximately 220 grams) which were separated into 4 experimentais batches: control group (T) [n = 6], diabetic lot treated with quercetin (DQ) [n = 6], quercetin and cinnamon treated diabetic lot (DQC) [n = 6], a non-diabetic lot treated with quercetin (Q) [n = 6] and a non-diabetic lot treated with quercetin and cinnamon (QC) [n = 6]. This study followed the guidelines of ethics on the animals used in experiments.

Administration of Streptozotocin

The induction of diabetes in the DQ and DQC lots was achieved by a single intraperitoneal injection (IP Inj) of STZ (Sigma ST Louis, Mo) at a dose of 45 mg/kg of body weight, i.e., a volume of 1 ml/kg. Streptozotocin was prepared extemporaneously in 0.1 M citrate buffer (pH 4.5). Lots Q and QC received only one IP Inj of the citrate buffer.

Administration of quercetin and cinnamon

Quercetin used for the treatment of rats is a yellow powder. The preparation of the corresponding dose depends on the weight of the rats at 5 mg/kg. Cinnamon is in the form of ocher powder. To prepare the correct dose, a precision scale was used to measure the weight of the rat 2g of cinnamon per

1kg of body weight. Quantified doses are added to Eppendorf tubes to be dissolved with 1 ml, 0.9% saline per kg body weight. The start of treatment with quercetin and cinnamon begins on the 7th day after the induction of diabetes and is administered by gastric gavage of rats for 7 days (duration of treatment). The treatment with cinnamon is used for lot D, Q, C, and Q, C every other day of the total administration period of 7 days.

The quercetin that we used is the Quercetin ≥95% (HPLC), solid 2- (3,4dihydroxyphenyl). The cinnamon we used is Natrol Cinnamon Extract 1000mg 80 tablets, which is composed of cinnamon bark extract, calcium phosphate dibasic, stabilizer (cellulose), anti-caking agents (stearic acid, silicon dioxide, carboxymethylcellulose, magnesium stearate, methylcellulose, glycerin.

Open-field test (OF)

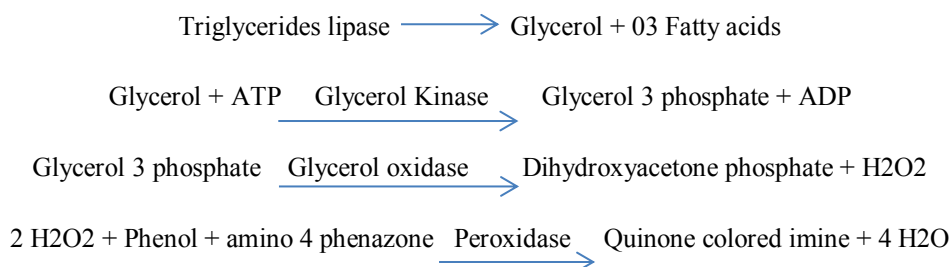
The Open Field test, originally described by Hall in 1934, was developed to measure differences in emotional reactivity in rats. The open-field test is performed for 5 minutes and the animal is placed in the center of a device (Sáenzet et al., 2006). Its displacement allows measuring the number of squares traversed as well as the time spent in each zone. Consequently, this test indicates locomotor activity and anxious behavior respectively. The latter is more noticed when the rat spends more time in the peripheral zone. As for the central zone, its exploration represents a sign of less anxiety.

Determination of the glycemic profile

During the experiment, the determination of the glycemic profile was preceded in two evolutionary and precise periods in all the rats included in the study. For this step, a manual glucometer (ONE TOUCH ultra®) was available to instantly measure blood glucose (expressed in g/l) from the caudal vein (Hiramatsu et al 2002) of each rat at day 4 and 14.

Measurement of triglycerides

Enzyme techniques are used by most laboratories. They are based on the enzymatic dosage of glycerol released after the action of lipase. The most used technique is that using the oxidase - peroxidase couple:



The colorimetric reading was made at 540 nm and normal levels were considered when <1.50 g/l. To establish a diet and/or treatment, the pathological threshold was equal to or greater than 2 g/l.

Statistical treatment of the data

The results were represented as mean and standard error (Mean ± SEM). The comparison between the different groups was performed by student t-test analysis. The statistical analysis of the data was performed using the PRISM software (Version 6.0).

Results

Blood glucose Level

During this experiment, blood glucose (g/l) was measured on day 4 and day 15. Streptozotocin caused highly significant hyperglycemia ($P < 0.001$) from the 4th day of the experiment in the diabetic quercetin (DQ) batch as well as the quercetin cinnamic diabetic (QCD) batch compared to the control group (T). After administration of the antioxidants, the two diabetic lots (DQ) and (DCQ) reveal a very significant decrease ($P < 0.01$) of the blood glucose level in day 15 compared to that of day 4.

Variation of the open field test parameters

The results obtained in Figure A show a significant decrease in the distance crossed by non-diabetic lots treated with quercetin (NDQ) and diabetic ones treated with cinnamon and quercitrin (DCQ). Similarly to the non-diabetic batch treated with cinnamon and quercetin, it shows a very significant decrease between the 7th and 14th day.

Regarding the 2nd parameter, which is the number of rectifications expressed in Figure B, a significant decrease ($P < 0.05$) is noticed on the 14th day of the diabetic batch treated with quercetin (DQ) compared to the 7th day.

The figure shows a very significant decrease ($P < 0.01$) for the non-diabetic lot treated with cinnamon and quercetin (NDCQ) and a highly significant decrease ($P < 0.001$) for the diabetic lot treated with cinnamon and quercetin (DCQ) at the 14th day compared with the 7th day.

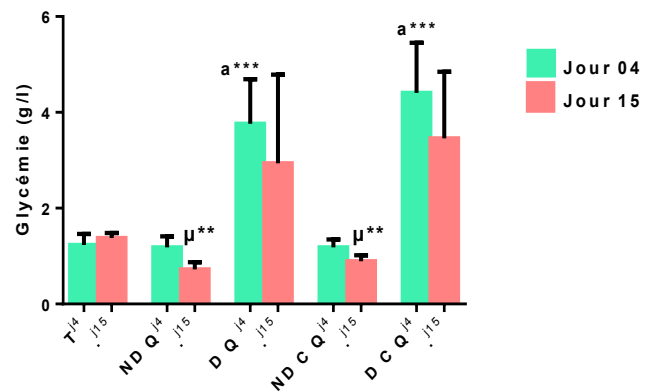


Figure 1 Changes in Glycemic Levels at Day 04 and 15 in the control group (T), Non-diabetic Treated with Quercetin (ND Q), Diabetic Treated with Quercetin (DQ) Rats, Non-Diabetic Rats treated with Cinnamon and Quercetin (ND CQ), diabetic rats treated with cinnamon and quercetin (DQC). a: Comparison between the control group and one of the batches; b: Comparison between non-diabetic treated lot and diabetic treated lot; μ : Comparison between days before and after treatment; Ns (Not significant difference) ($P > 0.05$; * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$)

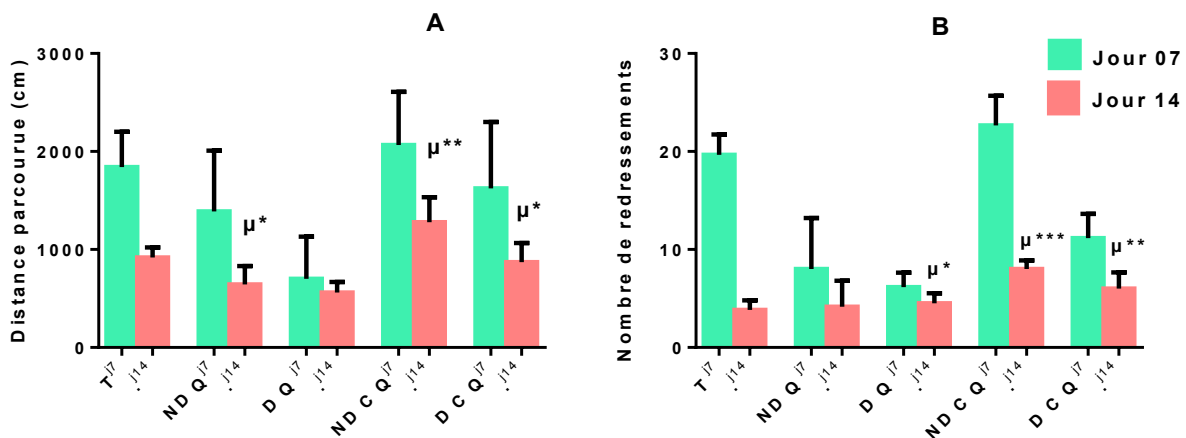


Figure 2 Variation of open field parameters in control (T), non-diabetic quercetin-treated (NDQ), diabetic quercetin-treated (DQ), non-diabetic cinnamon-treated and non-diabetic quercetin-treated (NDC Q), and diabetic rats treated with cinnamon and quercetin (DCQ). A; distance crossed by B; number of adjustments. Ns (Not significant difference) ($P > 0.05$; * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$)

Triglycerides

Triglyceride (expressed in g/l) was measured on the 15th day. The figure shows that a lot of diabetic rats treated with quercetin (DQ) indicated a significant increase ($P < 0.05$) compared with the batch of control rats (T) and a significant increase ($P < 0.05$) in the batch of diabetic rats treated with quercetin (DQ) compared to the non-diabetic lot treated with quercetin.

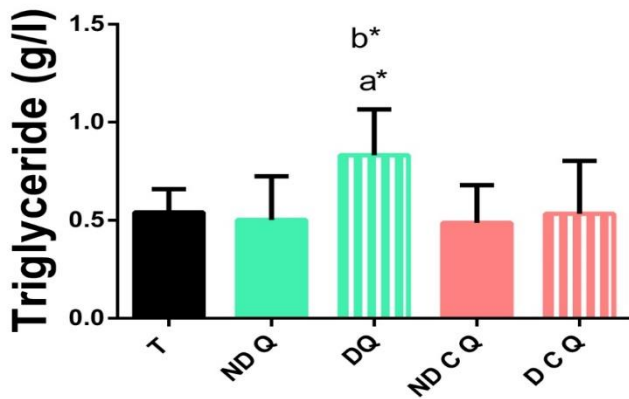


Figure 3 Variation of triglyceride in control (T) rats, non-diabetic quercetin-treated (NDQ), diabetic quercetin-treated (DQ), non-diabetic, cinnamon and quercetin-treated (NDC Q) diabetic rats treated with cinnamon and quercetin (DCQ). The results are expressed as mean \pm SEM ($n = 6$). Ns (Not significant difference) ($P > 0.05$; * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$)

Discussion

Diabetes and depression are frequent pathologies whose impact on the lives of individuals is important. The number of people with diabetes has been estimated at 2.9 million. People with diabetes are much more exposed to mental suffering, especially depression (Thiebaut 2010).

Diabetes is defined as chronic hyperglycemia, which is a fasting blood glucose level above 1.26 g/l (7mmol/l) twice (Grimaldi 2000). The use of medicinal plants plays an important role in the treatment of diabetes mellitus, many populations believe enormously in the effectiveness of these plants. Ethno-pharmacological and experimental studies have confirmed this property relating to plants to be able to control the glycemia of diabetics (Marleset Norman, 1994). The search for natural active ingredients from medicinal plants that can treat the metabolic disorders of diabetes is of great interest to health. Many herbs are traditionally considered as anti-diabetic drugs, some of which are at the origin of the development of drugs such as metformin thanks to Galega officinalis (Witters 2001). Our results showed that the STZ injection (45 mg/kg) causes highly significant hyperglycemia ($P < 0.001$) after 72 hours of injection in diabetic rats treated with quercetin and in diabetic rats treated

with cinnamon and quercetin which corresponds with the results of Daisy et al (2012), explaining this mechanism by direct toxicity on cells resulting in necrosis after 48 to 72 hours and causing permanent hyperglycemia.

The obtained results show a very significant decrease in the quercetin-treated rats which correspond with the results of Scalbert et al (2005) according to which, the polyphenols can have different actions on the peripheral tissues leading to a decrease in blood glucose, inhibition of gluconeogenesis and adrenergic stimulation of glucose uptake.

Cinnamon is known to have anti-diabetic properties; it is also perceived as an antioxidant with anti-inflammatory and anti-bacterial properties (Aggarwal and Sung 2009). In a metabolic syndrome model obtained using a high fructose diet, insulin resistance in animals is decreased by administration of 300 mg of aqueous extracts of cinnamon/day (Qin et al 2004). On the genetic model of diabetic rats, the sensitivity to insulin is increased, and the hyperglycemia regulated by the administration of 50 to 200 mg of aqueous extracts of cinnamon by the mechanism of action of the polyphenols of cinnamon on the cascade of Insulin signaling according to (Cao et al 2007).

Khan et al (1990) reported that the water-soluble compound of cinnamon potentiates insulin activity, and can improve the characteristic signs and symptoms of diabetes and cardiovascular diseases associated with insulin resistance. The insulin-like effect of cinnamon was initially attributed to its high chromium content, but no correlation could be established between chromium levels in cinnamon and its insulin-like activity. After this demonstration, 49 extracts of herbs, spices, and medicinal plants were evaluated to see how far they were insulin-like. Amongst the most effective compounds are cinnamon and green tea. (Broadhurst et al 2000).

Cinnamon is very rich in the cinnamic aldehyde. This volatile phenolic compound with antioxidant power has a quantity of dry matter that may exceed 17000 mg per 100 g (Shan et al., 2005). An in vitro study on human blood samples has shown that cinnamic aldehyde can decrease the activity of an enzyme associated with the onset of inflammatory or allergic reactions (such as asthma, allergic rhinitis, and psoriasis) (Prasad et al 2004).

This extract can also reduce blood glucose and lipid levels in chemically diabetic rats. It increases the level of circulating insulin and restores the activity of plasma enzymes (Subash 2007). Cinnamic acid and its derivatives have a variety of pharmacological properties including antioxidant and hypoglycemic activity (Duke 1992).

2-Alkoxydihydrocinnamate functions as a peroxisome proliferator-activated receptor (PPAR) agonist. In genetically diabetic (ZDF) rats, this compound leads to a reduction in blood glucose and triglyceride levels (Martin et al 2006).

The naphthalenemethyl ester; a derivative of dihydroxyhydrocinnamic acid, normalizes blood glucose in chemically or genetically diabetic rats and dramatically increases glucose transport by activating translocation of GLUT-4 (Kim et al 2006).

P-methoxycinnamic acid causes a decrease in the concentration of blood glucose and normalizes the activity of glucose-6-phosphatase, hexokinase, glucokinase, phosphofructokinase, glycogen, and glucose- 6-phosphate (Adisakwattana et al., 2005).

Recently, the polyphenolic polymers responsible for the potentiating effect of insulin have been identified in aqueous extracts of various kinds of commercially available cinnamon (Anderson et al 2004).

Stress is among the most important factors that negatively affect neurogenesis based on a recently developed concept that polyphenols are positive modulators of neurogenesis and stress resistance factors. Several studies in both animals and humans have reported the benefits of flavonoid intake and supplementation or on mental health. The administration of quercetin to animals undergoing acute stress suppresses activation of the hypothalamic-pituitary-adrenal (HPA) axis, which is a major component of the stress response and plays a major role in the etiology of stress-related pathologies (Roussel et al 2013).

Lots of researches have shown the hypoglycaemic effect of several plants containing polysaccharides, terpenes, flavonoids, and several other compounds (Sarkhail et al 2007). Developed by Hall and Ballechey, the open field is used to assess the anxiety-type emotional state and the level of locomotor and exploratory activity of the animal. The experiment is based on the natural aversive behavior of the animal concerning the discovered environments.

This test evaluates the reaction of an animal to a new and spacious environment. It creates a conflict situation between the animal's natural tendency to explore this new environment and its aversion to open spaces.

As a result, normal animals tend to spend more time in the corners and periphery of the device than in the center, which is then considered the most anxiety-provoking area (Crawley 1999; Prut and Belzung 2003; Elizalde et al 2008).

Our results highlight the significant decrease in distance crossed as well as the number of recoveries by quercetin-treated diabetic rats and diabetic rats treated with cinnamon and quercetin whose anxiety is the main cause. In agreement with the work done by Schmitt and Hiemke (1998) and Prut and Belzung (2003) who reported that the reduction in distance crossed in the device by stressed rats indicates a decrease in exploratory activity characteristic of a higher level of anxiety in rats.

Because of these observations, the relationship between diabetes and triglycerides is born from hormone insulin. Secreted by the pancreas, it regulates glucose levels in

the blood (blood glucose). In diabetics, insulin production is low or zero. The glucose level goes up; it's the hyperglycemia. Since triglycerides result from the breakdown of glucose, their level is also higher in diabetes: it is called hypertriglyceridemia.

Conclusions

The conducted study consisted of mounting experimental diabetes in adult female rats of the Wistar strain, caused by a single intraperitoneal injection containing streptozotocin at 45 mg/kg, which induced type 1 diabetes accompanied by neurobehavioral disturbances and also a decrease in weight as well as changes in lipid parameters. As a therapy, we opted for a treatment based on natural antioxidants of cinnamon and quercetin to see their remedial effects on the various complications related to experimental diabetes. The results show that these molecules stimulate the restorative responses of the body by limiting the damage caused by diabetes, prevent hyperglycemia, and restore weight loss. Herbal medicine offers solutions to heal with plants; it is a solution both alternative and complementary to conventional medical treatments, increasingly popular, and whose effectiveness is increasingly recognized.

Conflict of Interest

The authors declare no conflict of interest.

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