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The action of a natural polyphenol on diabetic animals developing neuro-behavioral and cognitive disorders

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Abstract
The aim of the present research was to evaluate the effects of a natural polyphenol, the Hesperidin, on induced diabetic wistar rats, on their neuro-behavioral alterations and movement functions. Four series of rats were used in the assays representing the control, and the treated series (Hesperidin, Streptozotocin and Hesperidin with Streptozotocin). After inducing the diabetes, the animals were exposed individually to the labyrinth in cross heightened test for a period of 5mn. Results of The test showed a slowing down in the movements, flexibility and a high level of anxiety on the diabetic rats. Thus, our results confirm the capacity of hesperidin as an antioxidant to reduce and to correct neurobehavioral and locomotion disorders related to diabetes and its complications by neutralizing free radicals generated by this metabolic disease.

Keywords: Anxiety, diabetes, hesperidin, streptozotocin

1. Introduction
The diabetes is a complex and progressive metabolic disease, characterized by a chronic hyperglycemia, resulting from a defect of the insulin secretion or its action or these both anomalies, with differed effects on the central nervous system and peripheral neuronal [1]. It was confirmed that diabetes induces adverse changes in the central nervous system, causing neuro-behavioral disorders, depression and cognitive dysfunction [2, 3, 4]. Diabetes also stimulates the increase in the activity of hypothalamic-pituitary-adrenal, consequently affects the stress response [5, 6]. Also it causes alterations in vessels, eyes and peripheral nerves, as traduced by the frequency of neuropathic pain in diabetics [7] and a peripheral neurological deficit induced by a neuronal degeneration and slowing nerve impulses [8]. Therefore the implication of diabetes to psychiatric manifestations; such as depression [7], behavioral disorders and anxiety [9], cognitive dysfunction [10, 11] and a slower movement [12, 13], were approved. As well the anxious behavior of a high level was showed in the elevated plus-maze [10, 14] and by the open field tests [15]. Diabetes involves several factors, such as metabolic disorders, vascular complications and the accumulation of free radicals [16, 17, 18]. In diabetic animals and in patients with type1 and type2 high levels of glucose, in the extra and intracellular environments, was defined as an imbalance between pro-oxidant and antioxidant [19]. Oxidative stress has been implicated to be as the main insidious in the genesis of various chronic diseases and degenerative complications by inducing either by the excessive production of reactive oxygen species or nitrogen or a depletion of antioxidant defense capabilities [20]. Therefore it is hypothesized that administration of antioxidants, as adjuvant therapy [21] to diabetic patients could reduce the risk of developing neuro-behavioral and cognitive disorders. To confirm this hypothesis, we assessed a contribution of an antioxidant for the prevention of the abnormal locomotors, behavioral and cognitive functions in induced diabetic rats with Streptozotocin and then treated with a natural polyphenol, Hesperidin. The evaluation of the neuro-behavioral and movements of Hesperidin treated rats were conducted using the labyrinth in cross heightened test.

2. Materials and Methods
2.1 Rearing rats
Wistar rats weighting 200±20g were obtained from Pasteur Institute, Algiers. They have been reared in the rearing house of the Department of Biology, University of Annaba inside polyethylene cages with a mean temperature of 25±2 °C, standardized photoperiod and

humidity. Rats were supplied with water and fed on standard diet made up in the form of rods produced by locally.

2.2 Rat treatments

The present rats were divided on equal four groups; The control group known as control vehicle (CV), treated group with Hesperidin (CHS), Group of diabetic rats inducted with Streptozotocin, considered as diabetic vehicle (DV) and the group rats treated with Hesperidin + Streptozotocin represent the (DHS). The CV received daily saline solution of NaCl 0.9% at 1ml/kg. Hesperidin CHS group, the rats received Hesperidin at dose of 50 mg/kg daily during 21 days diluted in 1ml/kg of NaCl 0.9%. Induction of diabetes in the rats of DV was done by a single intraperitoneal injection of Streptozotocin [Sigma ST Lowis, Mo] at the dose of 60 mg/kg body weight, with a volume of 1 ml/kg. Streptozotocin was prepared extemporaneously in a citrate buffer 0.1M (pH 4.5). After 72 hours of inducting diabetes in the group DHS, Hesperidin (50 mg/kg) was dissolved in NaCl and given by stomach tube to animals for a period of 21 days. Glycemia measurement of fasting glucose in blood was done at different periods (3, 7, 15 and 21 days) and was confirmed by the presence of glycosuria in urine by the use of dipstick bili labstix®.

2.3 The labyrinth in cross heightened test

The labyrinth in cross heightened is used to measure the degree of anxiety of the rodents [21]. The unit structure is heightened by 50 cm of the ground and consisted of four wooden arms; among which two opened of (50×10) cm opposing two closed others of (50×10) cm fixed in perpendicular way. Both closed arms rise of 40 cm of Plexiglas from their basis. The intersection of the four arms (central platform) measures 10cm [22, 23]. The test conducted for a period of 5 min by introducing individual rat in the central area of the unit, in the face of an open arm. It is known that the rat afraid of the empty and high spaces, its exploration in the open arms shows a less anxious behavior. In contrast more the animal is located in closed arms closed more its behavior is perceived as anxious [24]. After every test, the rat is put back in its cage and the labyrinth unit is cleaned with an alcoholic solution by wet paper towels and to be dried before the next test. The test parameters measured were movement activities, standing position, Also during the test spent time; in the open arms and the closed arms were measured and the number of entrance to the open arms and to the closed arms were counted. The anxiety level was estimated by the reference to the displacements in the two types of arms. It is considered that when the spent time in the central area is higher the rat's anxiety level will be lower.

2.4 Statistical analysis

The results were expressed in mean ± SEM and compared to control and analysed using Student's *t*-test, at $P<0.05$.

3. Results

3.1 Glycemia

Diabetes appeared in rats treated with Streptozotocin after 48 hours. Diabetes was checked at different periods in order to survey the increasing of glycemia. The rats subjected to treatment that inducts diabetes, their glycemia was increased significantly ($P<0.001$), from the day 3 after treatment with a glycemia recorded at more than 4g/l in day 21 (Table 1). However, this hyperglycemic state decreased significantly, after treatment of these animals with Hesperidin; therefore the glycemia was not regulated in comparison to control (Fig. 1).

Table 1: Concentration of blood glucose (mg/l) of the rat groups at different period. For each group, mean values followed by the same letter are not significantly different ($P< 0.05$).

Treated group rats	Concentration of blood glucose (mg/l) of the rat groups at different periods (days) after treatment			
	3 days	7days	15days	21days
Control vehicle (CV)	101±8 [a]	103±3 [a]	101±9 [a]	102±2 [a]
Treated control (CHS) with Hesperidin	101±5 [a]	108±3 [a]	111±9 [a]	108±2 [a]
Diabetic vehicle (DV) Treated with Streptozotocin	302±25 [b]	368±13 [b]	396±12 [b]	401±8 [b]
Treated with Streptozotocin and Hesperidin (DHS)	306±6 [b]	290±12 [b]	280±15 [b]	245±15 [b]

3.2 The labyrinth in cross heightened test

The labyrinths in cross heightened tests were evaluated by the spent time of the rats in different parts of the unit structure; closed arms, open arms and center part.

3.2.1 Treatment effects on spent time in the closed arms of the unit test

Results of the present test showed that the diabetic vehicle group DV spent more times in the closed arms compared to other groups (Figure 1). This traduces the high anxiety of these rats. After treatment the rats with Hesperidin (CHS), it was noticed the rats spent significantly less time in the closed arms compared to the control (DV). However this isolation in the closed arms was significantly higher compared to control (CV) which spent short time in this area (Figure1).

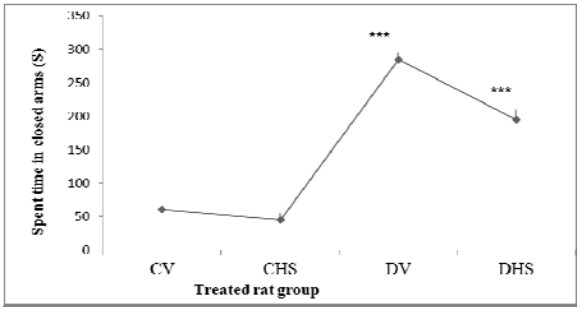

Fig 1: The spent time (s) in the closed arms by the rats of different treated groups [Treated rats (CV, CHS, and DHS) compared to the control (CV) ***= p< 0.001].

3.2.2 Treatment effects on spent time in the open arms of the unit test

Results of the present test showed that the Control group of rats spent much time in the open arms. Therefore the treated group with Hesperidin (CHS) spent more time compared to the other groups even the control one (Figure 2). The treated groups (DV and DHS) rats refused to spent time in the same place and showed a trouble in their behavioral movement.

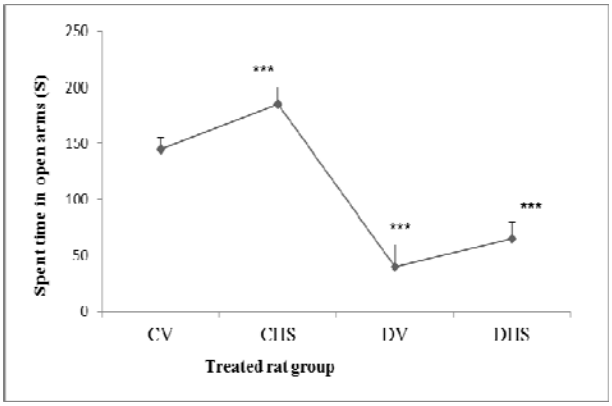

Fig 2: The spent time (s) in the open arms by the rats of different treated groups. [Treated rats (CV, CHS, and DHS) compared to the control (CV) ***= p< 0.001].

3.2.3 Treatment effects on spent time in the unit center test

Results showed that the diabetic vehicle group DV spent fewer times in the center part of the unit compared to other groups (Figure 3). This traduces the high anxiety of these rats that moved everywhere. The treated rats with hesperidin (CHS), presented stability in their movement by staying in the center area; where the spent time was not significantly different to the control one (Figure 3).

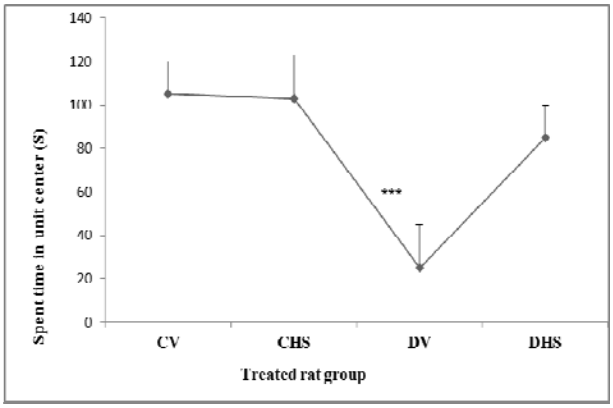

Fig 3: The spent time (s) in the unit center by the rats of different treated groups. [Treated rats (CV, CHS, and DHS) compared to the control (CV) ***= p< 0.001].

4. Discussion

The objective increase in diabetic rats treated with Streptozotocin was traduced with hyperglycemia after 24 hours compared with control group and these results concord with previous studies [20, 21, 15]. The administration of the Streptozotocin has inducted the fast destruction of pancreatic ß cells in Langherans islands of the treated rats. This effect lead to a change of the insulin secretion translated by a rise of the glycemia and a decrease of the absorption of the glucose in peripheral tissues; such as the skeletal muscles, the liver and the adipose tissues [22], The control of the glycogen metabolism; in the liver by an inter conversion between the activated forms and not activated by glycogen synthetase, was explained by activation of enzymes [23] and an increase of the neoglucogenesis and the production of hepatic glucose [24]. The treatment by the Hesperidin induces a decrease of the glycemia level of the diabetic rats. This result confirmed the previous study tested in serum glucose of rats. Blood glucose in the presence of this antioxidant has returned to normal level as that of the control and confirmed previous work [25]. Similar results have been reported by after treatment of *Ruta graveolens* and *rutin* with nicotinamide/streptozotocin diabetic rats [8].

Oxidative stress is considered as the main insidious of various chronic diseases and degenerative complications, like diabetes. It is induced either by the excessive production of reactive oxygen species or nitrogen or a depletion of antioxidant defense capabilities [13, 26, 27]. Several bio-flavonoids present in plants and in components of the human food were described to correct the hyperglycemia in the sweet diabetes, by allocating the glucose transport [28, 29], for their properties of the insulin-like function [30] and of the insulin analogue at the receptors [31].

The analysis of these results of the tests traduced by the level of anxiety, locomotor function and mental flexibility, showed an increase in spent time of diabetic and diabetic treated rats. Similar results were obtained when male wistar rats were treated with a natural flavonoid, the Quercetin [32]. This it demonstrates a high level of anxiety and a slowdown in motor function [13]. It was reported too music is used as a therapy that modulates a combined predator and noise stress induced anxiety-like behavior in male wistar rat [33]. Hespéridine, bioflavonoids of citrus fruits, present biological and pharmacological properties. It exhibits an anti-inflammatory, anti-carcinogenic and anti-oxidant activity [34]. In this study, diabetic rats showed a stressful behavior traduced by the decrease of the spent time in the open arms. Many studies used this behavioral criterion as a parameter of anxiety and confirmed these results [35, 36]. A deficiency of the cognitive function was observed at diabetic patients as well as at animals [37]. The treatment by the Hesperidin to diabetic rats was proposed to modulate the anxious behavior. This got oxidative capacities in the modulation of the cerebral neuronal transmission and the HPA activation. Hesperidin was reported to ameliorate the behavioral and biochemical indicators of mice and that by modulating the nitrergic pathway [38]. These results support the findings of previous studies that also showed an improvement in the number of entry and the time spent in the open arms of the treatment after repeated Hesperidin treatment. It is concluded that the present study showed a high level of anxiety and a slowdown in locomotion and mental flexibility and modulate the disorders related to diabetes [36].

5. Conclusion

The obtained results of the labyrinths in cross heightened tests confirm the capacity of Hesperidin to correct neurobehavioral disorders related to diabetes and its complications by neutralizing free radicals, of cell aging and apoptosis. It also has the capacity to control the neuro-degenerative symptoms. Therefore it is suggested that Hesperidin can be used as a therapeutic complement against neuro-behavior disorders.

6. References

1. Permutt MA, Wasson J, Cox N. Genetic epidemiology of diabetes. Journal of Clinical Investigation. 2005; 115:1431-1439.
2. Anderson RJ, Grisby A, Freedland KE, de Groot M, McGill JB, Clouse RE. Anxiety and poor glycemic control: a meta-analytic review of literature. International Journal of Psychiatry and Medicine. 2002; 32(3):235-47.
3. Alvarez EO, Beauquis J, Revsin Y, Banzan AM, Roig P, De Nicola AF, *et al*. Cognitive dysfunction and hippocampal changes in experimental type1 diabetes. Behavioral Brain Research. 2009; 198:224-230.
4. Reijmer YD, Van Den Berg E, De Bresser J. Accelerated cognitive decline in patients with type 2 diabetes: MRI correlates and risk factors, Diabetes/Metabolism Research Review. 2011; 27(2):195-202.
5. Saravia FE, Gonzalez SL, Roig P, Alves V, Homo-Delarche F, De Nicola AF. Diabetes increases the expression of hypothalamic neuropeptides in a spontaneous model of type I diabetes, the nonobese diabetic (NOD) mouse. Cellular and Molecular Neurobiology. 2001; 21:15-27.
6. Chan O, Inouye K, Riddell MC, Vranic M, Matthews SG. Diabetes and the hypothalamo-pituitary adrenal (HPA) axis. Minerva Endocrinology. 2003; 28:87-102.
7. Schwarz PE, Li J, Lindstrom J, Tuomilehto J. Tools for predicting the risk of type2 diabetes in daily practice. Hormone and Metabolism Research. 2009; 41:86-97.
8. Gispen WH, Biessels GJ. Cognition and synaptic plasticity in diabetes mellitus. Trends Neuroscience. 2000; 23(11):542-548.
9. Oldroy dJ, Banerjee G, Heald A, Cruickshank A. Diabetes and ethnic minorities. Postgraduate Medicine Journal. 2005; 81:486-490.
10. Adeghate E, Schattner P, Dunn E. An update on the etiology and epidemiology of diabetes mellitus. Annals of New York Academy Science. 2006; 10(84):1-29.
11. Sima AA, Zhang W, Muzik O, Kreipke CW, Rafols JA, Hoffman WH. Sequential abnormalities in type1 diabetic encephalopathy and the effects of C-Peptide. Review of Diabetes Study. 2009; 6(3):211-222.
12. Ramanathan M, Jaiswal AK, Bhattacharya SK. Differential effects of diazepam on anxiety in streptozotocin induced diabetic and non-diabetic rats. Psychopharmacology (Berlin).1998; 135(4):361-367.
13. Brands AM, Biessels GJ, De Haan EH, Kappelle LJ, Kessels RP. The effects of type1diabetes on cognitive performance: A meta-analysis. Diabetes Care. 2005; 28(3):726-735.
14. Miyata S, Yamada N, Hirano S, Tanaka S, Kamei J. Diabetes attenuate psychological stress-elicited 5-HT secretion in the prefrontal cortex but not in the amygdala of mice. Brain Research. 2007; 1147:233-239.
15. Bensaoula DA, Boukhris N, Tahraoui AK. Hesperidin effects on behavior and locomotor activity of diabetic Wistar rat. African Journal of Biotechnology. 2016; 15(45):2572-2577.
16. Biessels GJ, Kerssen A, de Haan EH, Kappelle LJ. Cognitive dysfunction and diabetes: Implications for primary care. Primary Care Diabetes. 2007; 1:187-193.
17. Kucukatay V, Agar A, Gumuslu S, Yargicog˘lu P. Effect of sulfur dioxide on active and passive avoidance in experimental diabetes mellitus: Relation to oxidant stress and antioxidant enzymes. International Journal of Neuroscience. 2007; 117:1091-1107.
18. Tuma I. Diabetes mellitus and cognitive impairments. Vnitrni Lekarstvi. 2007; 53:486-488.
19. Stewart R, Liolitsa D. Type 2 diabetes mellitus, cognitive impairment and dementia. Diabetes Medicine. 1999; 16: 93–112.
20. Schaalan M, El-Abhar HS, Barakat M, El-Denshary ES. Westernized-like-diet-fed rats: effect on glucose homeostasis, lipid profile and adipocyte hormones and their modulation by rosiglitazone and glimepiride. Journal of Diabetes Complication. 2009; 23:199-208.
21. Favier A. Le stress oxydant Intérêt conceptuel et expérimental dans la compréhension des mécanismes des maladies et potentiel thérapeutique. Laboratoire de recherche, lésions des acides nucléiques et département de biologie intégrée au CHU de Grenoble, France. 2003; 2:50-136.
22. Beck-Nielsen H. Insulin resistance: organ manifestations and cellular mechanisms. Ugeskr Laeger. 2002; 164:2130-2135.
23. Gold AH. The effect of diabetes and insulin on liver glycogen synthetase activation. Journal of Biology and Chemistry. 1970; 245:903-905.
24. Raju J, Gupta D, Rao AR, Yadava PK, Baquer NZ. Trigonella foenum graecum (fenugreek) seed powder improves glucose homeostasis in alloxan diabetic rat tissues by reserving the altered glycolytic, gluconeogenic and lipogenic enzymes. Molecular and Cellular Biochemistry. 2001; 224:45-51
25. Ahmed OM, Abdel-Moneim A, Abulyazid I, Mahmoud AM. Anti-hyperglycemic, anti hyperlipidemic and antioxidant effects and the probable mechanisms of action of *Ruta graveolens* and rutin in nicotinamide/streptozotocin diabetic albino rats. Diabetologia Croatica. 2010; 39:15-32.
26. Jung UJ, Le MK, Jeong KS, Choi MS. The hypoglycemic effects of hesperidin and naringin are partly mediated by hepatic glucose regulating enzymes in 57BL/KsJ-db/db mice. Journal of Nutrition. 2004; 134:2499-2503.
27. Moree SS, Kavishankar GB, Rajesha J. Antidiabetic effect of secoisol ariciresinol diglucoside in streptozotocin induced diabetic rats. Phytomedicine. 2013; 20(3-4):237-245.
28. Ong KC, Khoo HE. Insulino mimetic effects of myricetin on lipogenesis and glucose transport in rat adipocytes but not glucose transporter translocation. Biochemistry and Pharmacology. 1996; 51:423-429.
29. Hsu FL, Liu IM, Kuo DH, Chen WC, Su HC, Cheng JT. Antihyperglycemic effect of puerarin in streptozotocin-induced diabetic rats. Journal National Production. 2003; 66:788-792.
30. Alp HS, Varol MM, Celik M, Altas O, Evliyaoglu O, Tokgoz MH *et al*. Protective effects of beta glucan and gliclazide on brain tissue and sciatic nerve of diabetic rats induced by streptozosin. Experimental Diabetes Research. 2012; 7:243-247.
31. Shisheva A, Shechter Y. Quercetin selectively inhibits insulin receptor function *in vitro* and the bioresponses of insulin and insulinomimetic agents in rat adipocytes. Biochemistry. 1992; 31:8059-8063
32. Bouhali IE, Tayaa H, Tahraoui AK. Quercetin, a Natural Flavonoid, Mitigates Fenthion Induced Locomotor Impairments and Brain Acetylcholinesterase Inhibition in Male Wistar Rat. Middle-East Journal of Scientific Research. 2015; 23(1):55-58.
33. Attoui N, Bouhali IE, Tayaa H, Habbachi W, Bairi A,

Tahraoui AK. Music Therapy Modulates Combined Predator and Noise Stress Induced Anxiety-Like Behavior in Male Wistar Rat. Middle-East Journal of Scientific Research. 2015; 23(3):374-377.
34. Bok SH, Lee SH, Park YB, Bae KH, Son KH, Jeong TS, Choi MS. Plasma and hepatic cholesterol and hepatic activities of 3-hydroxy-3-methyl-glutaryl-CoA reductase and Acyl CoA: cholesterol transferase are lower in rats fed citrus peel extract or a mixture of citrus bioflavonoids. Journal of Nutrition. 1999; 129:1182-1185.
35. Choi MS, Do KM, Park WB, Jeon SM, Jeong TS, Lee YK, *et al*. Effect of naring in supplementation on cholesterol metabolism and antioxidant status in rats fed high cholesterol with different levels of vitamin E. Annals of Nutrition and Metabolism. 2001; 45:193-201.
36. Strachan MWJ, Frier BM, Deary IJ. Type 2 diabetes and cognitive impairment. Diabetic Medicine. 2003; 20:1-2.
37. Brands AM, Biessels GJ, Kappelle LJ, de Haan EH, de Valk HW, Algra A *et al*. Cognitive functioning and brain MR1 in patients with type1 and type2 diabetes mellitus: a comparative study. Dementia and Geriatric Cognitive Disorders. 2007; 23:343-350.
38. Viswanatha GL, Shylaja H, Sandeep VR, Santhosh K, Jagadeesh M. Hesperidin Ameliorates Immobilization-Stress Induced Behavioral and Biochemical Alterations and Mitochondrial Dysfunction in Mice by Modulating Nitrergic Pathway. International Scholar Research Network. 2012; 18:45-49.