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Morin (2′,3,4′,5,7-Pentahydroxyflavon) Antioxidant Effect in Streptozotocin-Induced Diabetic Rat Brain and Heart Tissues [*]

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Abstract: Diabetes mellitus is agreed to be among the biggest public health burdens seen at the world. Recently, the using natural products (flavonoids specially) in diabetes treatment saw a rise in interest due to insulin's and oral anti-diabetic medicines' unfavorable side effects. The present work is studying the beneficial effects of morin (2′,3,4′,5,7-pentahydroxyflavone) on antioxidant of tissues and lipid peroxidation status in diabetic and non-diabetic rats. Diabetes associated with elevation in reactive oxygen species and deficient in antioxidant activity, which is important aspects for pathogenesis of diabetes. The role of morin on the brain and heart antioxidant markers were estimated. The diabetic rats exhibited elevated levels of thiobarbituric acid reactive substances (TBARS), Nitric oxide (NOx) and glutathione (GSH) levels in brain and heart tissues when compared with healthy animals. The treatments using morin significantly stopped elevation in brain and heart TBARS and NOx levels. Oral administration of morin showed significant increase in GSH level in brain tissue. These results indicated that morin exerts antioxidative activity in diabetic rats.

Keywords: Diabetes, glutathione, morin, oxidative stress.

Morin (2′,3,4′,5,7-Pentahidroksiflavon) Streptozotosin ile İndüklenen Diyabetik Sıçan Beyin ve Kalp Dokularında Antioksidan Etkisi

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Öz: Diabetes mellitusun dünyada görülen en büyük halk sağlığı zorunluklarından biri olduğu kabul edilmektedir. Son zamanlarda, insülin ve oral anti-diyabetik ilaçların olumsuz yan etkileri nedeniyle diyabet tedavisinde doğal ürünler (özellikle flavonoidler) kullanımı artan bir ilgiye tanık olmuştur. Bu araştırma, diyabetik ve diyabetik olmayan sıçanlarda morinin (2',3,4',5,7-pentahidroksiflavon) doku antioksidanları ve lipid peroksidasyonu üzerindeki yararlı etkilerini incelemektedir. Artan reaktif oksijen türleri ve yetersiz antioksidan aktivite diyabet ile ilişkilidir, buda diyabet patogenezinde başlıca sorumludur. Beyin ve kalp antioksidan belirteçleri üzerinede morin'in rolü değerlendirildi. Diyabetik sıçanların beyin ve kalp dokularında normal sıçanlara göre tiyobarbitürik asit reaktif maddeleri (TBARS) ve nitrik oksit (NOx) düzeyleri daha yüksek, glutatyon (GSH) düzeyi ise daha düşük gözlendi. Morin muamelesi beyin ve kalp TBARS ve NOx düzeylerindeki artışı anlamlı olarak önledi. Ayrıca morin beyin GSH seviyesinde önemli artış gösterdi. Sonuçlar morin'in diyabetik sıçanlarda antioksidan aktivite gösterdiğini belirtmektedir.

Anahtar kelimeler: Diyabet, glutatyon, morin, oksidatif stres.

[*] *This study was produced from the master thesis.*

INTRODUCTION

The overexpression of oncogene genes, production of mutagen compounds, encouragement of atherogenic activity, occurrence of senile plaques, or inflammation are just a few of the factors that can lead to oxidative damage in a cell when there is an imbalance between the oxidant species and the antioxidant defense system. Cancer, neurodegeneration, cardiovascular illnesses, diabetes, and kidney ailments are appeared as a consequence of this imbalance (Pisoschi & Pop, 2015). Diabetes mellitus, also known as metabolic abnormalities, causes hyperglycemia, which is caused by a lack of insulin secretion, impact, or both. Type 1 diabetes is the most common type, which outcome by completely loss of the secretion of insulin and Type 2 that appears as a result of synergy between insulin and insufficient secretion of insulin (Hansen, 1998; ADA, 2008). Free radical production, particularly reactive oxygen species (ROS), is mediated by chronic hyperglycemia. Three primary methods can be used to explain the formation of ROS; autooxidation of glucose, activation of polyol pathway and protein glycation, accompanied by impaired antioxidant defense mechanisms which lead to oxidative stress that cause damage of cellular components (Bonnefont-Rousselot, 2002; Atlan et al., 2006). The defense system of antioxidants consisting of nonenzymatic (e.g., α-lipoic acid, cofactors, glutathione (GSH), trace elements, vitamins) and enzymatic (e.g., catalase, glutathione peroxidase, superoxide dismutase) players which present in all aerobic organisms to protect cells and tissues against oxidative damage. Using of different antioxidants in experimental diabetes models subjected to extensive scientific studies. Recently numerous compounds with antioxidant properties, especially those derived from plants, showed beneficial effects against diabetes and its complications (Fidan et al., 2009; Sankaranarayanan & Pari, 2011) and some compounds used as an approved antidiabetic agents have antioxidant activity (Güleç Peker et al., 2021).

Flavonoids are considered one of the most powerful antioxidants which were also used against oxidative stress in diabetes (Roghani & Baluchnejadmojarad, 2010; Srinivasan and Pari, 2012). Morin (2′,3,4′,5,7-pentahydroxyflavone) considered one of the flavonoids belonging to flavonols (Figure 1).

Isolated specially from plants of Moraceae (Xie et al., 2006). Morin known to have several records of biological and pharmacological activities (Lee et al., 2008; Sreedharan et al., 2009; Subash & Subramanian, 2009; Al-Numair et al., 2012). Moreover, even at high doses it has no toxic effects in animals (Yugarani et al., 1992). This study was conducted to explore morin antioxidant activity in streptozotocin (STZ) diabetic rats.

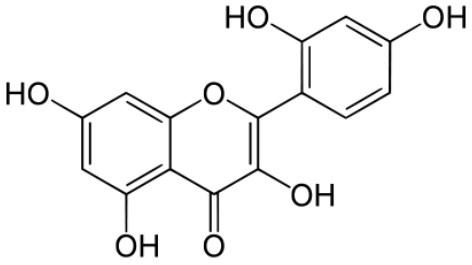

Figure 1. Morin structure.

MATERIAL AND METHOD

Chemicals and Reagents: Sigma Aldrich, St. Louis, USA, provided the STZ and all other compounds. The rest of the reagents were of analytical grade.

Experimental Animals: Male Wister rats, aged 2-3 months (180-230 g), were obtained from Refik Saydam Central Institute of Health (Ankara, Turkey) and kept under conventional conditions, including a 12/12 h light/dark cycle, a 22+2 °C ambient temperature, and free access to food and water. The Institutional Animal Ethics Committee at Gazi University (G.Ü ET-10.084) approved the procedure and rules for animal experimentation.

Induction of Diabetes: STZ was delivered intraperitoneally to overnight fasting rats (45 mg/kg) in 0.1 M cold sodium citrate buffer (pH: 4.5), normal animals were given only buffer. 72 hours after STZ injection, blood glucose levels were assessed. Diabetic rats are those whose blood sugar levels are greater than or equal to 200 mg/dL.

Experimental Design: The animals were placed into seven groups, each with six animals:

Group I: normal rats given only vehicle (carboxy methyl cellulose CMC 0.5%; 1mL/kg) (NC)
Group II: normal rats + morin (25 mg/kg) (N25)
Group III: normal rats + morin (50 mg/kg) (N50)
Group IV: diabetic control rats given only vehicle (DC)
Group V: diabetic rats + morin (25 mg/kg) (D25)
Group VI: diabetic rats + morin (50 mg/kg) (D50)

Treatment was given orally by gavage once daily for 21days. The rats were sacrificed in day 21 under ether anesthesia. Dissected brain and heart tissues were cleansed with ice cold 0.9 percent saline solution to move blood, then dried on filter paper and kept at 80 °C for biological analysis.

Biochemical Assays: The levels of thiobarbituric acid reactive substances (TBARS) in brain and heart tissues are used to assess lipid peroxidation (Buege & Aust, 1978). In brief, tissue samples were homogenized (Heidolph Diax 900 homogenizer, Germany) in ice-cold 150 mM KCl, then 1 mL of homogenate treated with 0.5 mL of 15% TCA for deproteinization then samples centrifuged at 2000 xg. 0.5 mL of 0.67% TBA and 10 µL of 1% BHT were added to supernatant for prevention further lipid peroxidation. After 10 min in water bath

samples cooled, absorbance read at 535 nm. TBARS concentrations expressed as nmol/g tissue.

Ellman (Ellman, 1959) was used to determine the GSH levels in the tissues. Tissues were homogenized in ice-cold 150 mM KCl, then combined with 0.75 mL of deproteinization solution (NaCl, metaphosphoric acid, EDTA) and centrifuged at 4000 xg for 20 minutes. The supernatant was then combined with 2 mL of 0.3 M NaH2PO4 and 0.2 mL of the DTNB (5,5'-dithio-bis-2-nitrobenzoic acid) reagent. At 412 nm, the absorbance was measured. GSH concentrations are measured in micromoles per gram of tissue.

Nitric oxide (NOx) measured by Griess assay which involves nitrate reduction by vanadium (III) chloride through acidic reaction of Griess (Miranda et al., 2001). Tissues homogenized (1:9) in phosphate buffer (0.1 M, pH7.0) and centrifuged for 15 min at 3500 xg at 4 °C. The supernatants were then treated with 0.25 ml of 0.3 M NaOH (0.5 ml). After 5 minutes of room temperature incubation, 0.25 mL of 5% (w/v) ZnSO4 was added for deproteinization. The mixture was then centrifuged at 3000 xg for 20 minutes, with the supernatants utilized in the Griess assay (Green et al., 1982). Absorbance read at 540 nm. NOx concentrations expressed as µmol/g tissue.

Statistical analysis: Statistical analyzing were carried out using SPSS package (version 13.0), which include ANOVA pursued by post hoc Tukey's test. The results are presented as the mean±SEM for six rats in each group. p-Values <0.05 are deemed significant.

RESULTS AND DISCUSSION

Antioxidants are substances or nutrients found in food that can stop or delay the body's oxidative damage. Free radicals are naturally produced by our body cells as they use oxygen, and they can harm our tissues. As "free radical scavengers," antioxidants stop and reverse the damage caused by these free radicals. Oxidative damage is a factor in a number of health issues, including cancer, diabetes mellitus, heart disease, and muscle degeneration (Nirmala et al., 2011).

STZ is a cytotoxic glucose analogue which enter β-cells of pancreas through the glucose 2 transporter and preferentially accumulates inside these cells (Tjälve et al., 1976). STZ (alkylating agent) methylnitrosourea moiety results in the death of these cells through fragmentation of the DNA. The cellular efforts for repairing DNA will lead to the overstimulation of poly (ADP-ribose) polymerase and that will be the reason for the depletion of cellular NAD+, thus the storage of ATP that in turn take the β-cells toward necrosis. Also, diabetogenic activity of STZ can be backed to its ability to the liberation of NO and ROS (Lenzen, 2008; Murata et al., 1999; Yamamoto et al., 1981). Persistent hyperglycemia leads to oxidative stress which considered the major factor in occurrence of diabetes complications (Bonnefont-Rousselot, 2002).

Free radicals generated due to chronic hyperglycemia which in turn leads to shortage in antioxidant defense systems which cause oxidative stress (Karasu, 1999). Lipid peroxidation (LP) is the reaction of free radicals like ROS with polyunsaturated fatty acids that will be responsible from lipid products formation such as TBARS (Lubin et al., 1972). LP is one of the most important mechanisms of cell damage leading to necrosis or apoptosis (Burton, 1989; Stark, 2005). The present study showed a significant elevation in diabetic rats TBARS levels of brain and heart. These values were obtained through experiments are in agreement with several studies (Bellamkonda et al., 2011; El Ghoul et al., 2012). The elevated TBARS levels in diabetic rats suggest that peroxidative damage may be an important part of the appearing complications of diabetes. In our study the morin significantly reduced the brain and heart tissues TBARS levels of the diabetic animals that can be because its scavenging capacity of the free radicals generated by ROS and prevent its deleterious effects.

The protection against oxidative stress includes enzymatic and non-enzymatic antioxidant systems. GSH is an important intracellular scavenger of free radicals, GSH acts by redox homeostasis balancing, free radicals quenching and through taking role in the reactions of detoxification (Matkovics et al., 1982). In diabetes depletion of NADPH through polyol pathway leads to shortage in GSH and subsequently decreases in GPx activity (Lorenzi, 2007).

Administration of morin (25 and 50 mg/kg) to normal rats didn't display notable difference in TBARS, GSH and NOx levels relative to normal control group in brain and heart tissues. STZ-diabetic rats exhibited a seriously raise in TBARS levels in all studied tissues ($p<0.05$). Morin administration (25 and 50 mg/kg) displayed varied degree of reduction in TBARS levels of brain and heart (Figure 2).

Brain GSH levels in diabetic control rats manifested significant decrease ($p<0.05$). Application of morin to diabetic rats failed to show any clear changes in D25, while increase in D50 group was significant ($p<0.05$), this activity reflects the strong antioxidant nature of this flavonoid. There was no obvious change in heart GSH levels among groups (Figure 3). This result is consistent with former studies (Maritim et al., 1999).

Earlier studies show variable information regarding impact of diabetes on the level's NOx. A significant reduction has been shown by many studies (Xie et al., 2006; Zhang et al., 2011), on the contrary, some other references revealed an increase in NOx levels as a consequence for induction of diabetes (Seven et al., 2004).

Upon our results NOx levels were raised in both brain and heart tissues of diabetic control rats in comparison with healthy animals. This height could be one of the reasons leads to β-cells damage during diabetes development (Welsh et al., 1994). Morin treatment lowered obviously ($p<0.05$) brain NOx levels in D25 and D50 groups when compared with diabetic control ($p<0.05$). In the heart tissue only D50 group showed a clearly decrease ($p<0.05$) in NOx levels (Figure 4). This improvement because of morin administration can be backed to either down-regulation of NOS gene expression or directly scavenging of NOx.

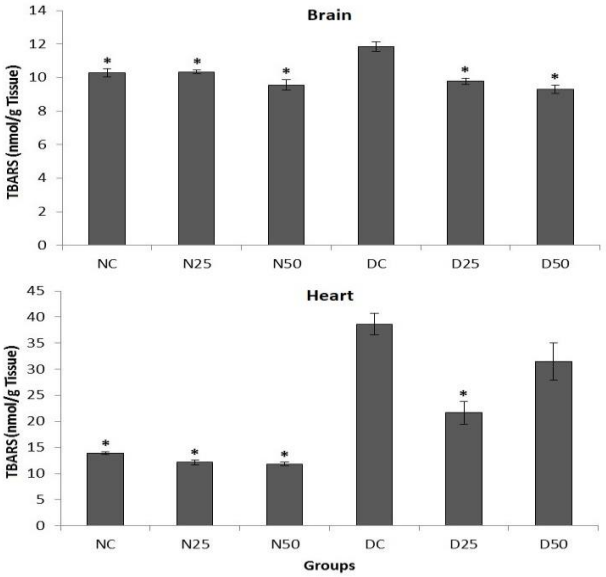

Figure 2. Morin treatment effects on TBARS in brain and heart tissues. *Significantly different from diabetic control rats at $p<0.05$. Data presented as mean±SEM (n= 6).

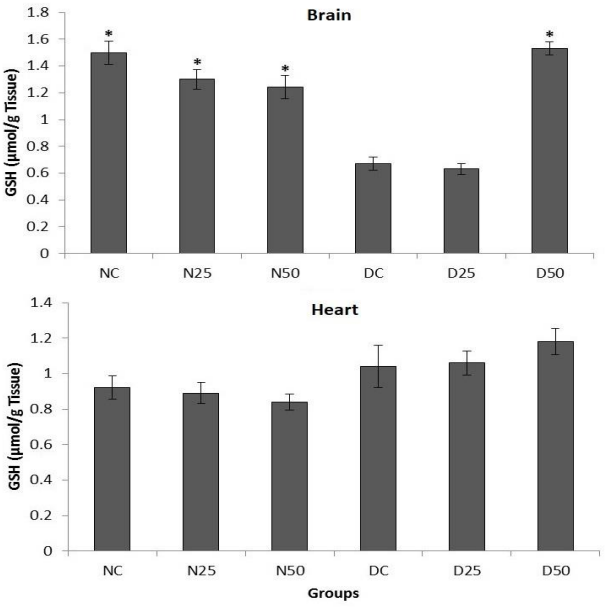

Figure 3. Morin treatment effects on GSH in brain and heart tissues. *Significantly different from diabetic control rats at $p<0.05$. Data presented as mean±SEM (n= 6).

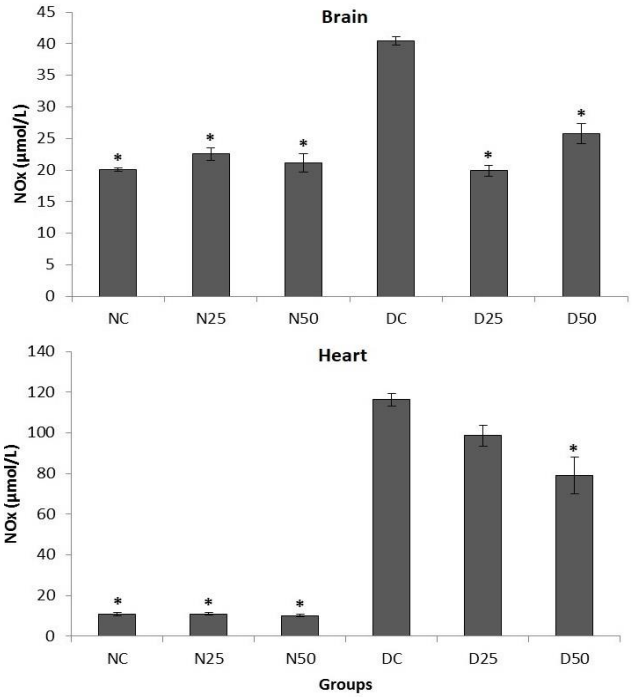

Figure 4. Morin treatment effects on NOx in brain and heart tissues. *Significantly different from diabetic control rats at $p<0.05$. Data presented as mean±SEM (n= 6).

CONCLUSION

Findings indicates that morin application to STZ-diabetic rats results in a considerable antioxidant activity. In terms of human health studies morin thought to be a good source in the alternative remediation of diabetes.

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