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Hesperidin alleviates inflammation in the metabolic syndrome model

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ABSTRACT

In metabolic syndrome, activated inflammatory signaling pathways trigger the release of proinflammatory cytokines. Nowadays, the use of natural bioactive compounds is trending as an alternative method for the treatment and management of metabolic syndrome. This study aimed to assess the potential effects of hesperidin in the metabolic syndrome model by analyzing the proinflammatory and anti-inflammatory cytokines in serum and liver. Rats were divided into 4 groups: Control (Rats were fed a standard chow diet and water *ad libitum*), hesperidin [Rats were fed hesperidin supplemented standard chow diet (1%, 10 g/kg feed) and water *ad libitum*] metabolic syndrome (Rats were fed standard chow diet with 10% fructose-added-drinking-water), and metabolic syndrome + hesperidin (Rats were fed a hesperidin-added standard chow diet (1%, 10 g/kg) with 10% fructose-added-drinking-water). Rats were sacrificed under ketamine/xylazine anesthesia, blood was obtained and liver tissues were removed. Tumor necrosis factor-alpha, interleukin-1 beta, interleukin-6, interleukin-10, and transforming growth factor-beta in the serum and liver were measured by enzyme-linked immunosorbent assay. In the metabolic syndrome group, higher tumor necrosis factor-alpha, interleukin-1 beta, and interleukin-6, but lower serum and liver interleukin-10 and transforming growth factor-beta were found in the serum and liver compared to the control group. In addition, in the metabolic syndrome + hesperidin group lower interleukin-1 beta and interleukin-6 but higher serum interleukin-10 and transforming growth factor-beta were found in the serum and liver compared to the metabolic syndrome groups. Consequently, hesperidin suppressed the serum and liver proinflammatory cytokine response and stimulated the anti-inflammatory cytokine response in the metabolic syndrome rat model.

Key words: cytokine; hesperidin; insulin resistance syndrome; liver; rat

Introduction

Metabolic syndrome is considered to be a major global public health crisis (AGGARWAL, 2010) and the prevalence of metabolic syndrome is increasing day by day (YARIM and KAZAK, 2016). Metabolic syndrome, also known as insulin resistance syndrome, syndrome X, hypertriglyceridemic waist, and the deadly quartet, represents a group of clinical and biochemical abnormalities including

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central obesity, hypertension, impaired blood lipid and glycemic parameters, insulin resistance, and atherogenic dyslipidemia (ROCHLANI et al., 2017; ZAFAR et al., 2019). Thus, metabolic syndrome adversely influences several body systems (SWARUP et al., 2022).

In metabolic syndrome, the activated inflammatory signaling pathways trigger the release of proinflammatory cytokines (YARIM and KAZAK, 2016). The proinflammatory cytokines released from macrophages within the enlarged adipose tissue are responsible for the development of atherosclerosis and coronary artery disease (ROCHLANI et al., 2017; SWARUP et al., 2022). Inflammation appears to be one of the main players in the initiation, progression, and transition of metabolic syndrome to cardiovascular disease (ROCHLANI et al., 2017). In addition, metabolic syndrome and a proinflammatory state may also trigger a spectrum of liver damage, by leading to steatosis that may progress to non-alcoholic steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma (SWARUP et al., 2022). It has been demonstrated that inflammatory signaling pathways are activated, and the release of proinflammatory and anti-inflammatory cytokines is altered in metabolic syndrome (YARIM and KAZAK, 2016; FARZAEI et al., 2019; NERI-NUMA et al., 2020)

Current studies (FARZAEI et al., 2019; YAMAGATA, 2019; NERI-NUMA et al., 2020) focus on flavonoid-rich diet nutrition in the prevention, mitigation, and treatment of metabolic syndrome, and/or its components. Furthermore, natural compounds and dietary elements have been indicated to possess benefits in the treatment of metabolic syndrome (ROCHLANI et al., 2017) and are used for therapeutic strategy in metabolic syndrome by targeting inflammation (FARZAEI et al., 2019; NERI-NUMA et al., 2020).

Hesperidin (3,5,7-trihydroxyflavanone 7-rhamnoglucoside, $C_{28}H_{34}O_{15}$), a bioflavonoid, is an abundant product of citrus fruits, and has a broad range of pharmacological features (GARG et al., 2001; LI and SCHLUESENER, 2017). LI and SCHLUESENER (2017) reviewed preclinical studies and clinical trials and found that they indicate the therapeutic effects of hesperidin in various diseases, including neurological disorders, psychiatric disorders, and cardiovascular diseases, cancers and others, according to its anti-oxidant, anti-inflammatory, insulin-sensitizing, and lipid-lowering features. A recent study showed that hesperidin ameliorates signs of metabolic syndrome and cardiac dysfunction via phosphorylating insulin receptor substrate 1, p-Akt and the glucose transporter 4 signaling pathway in a metabolic syndrome rat model (PRASATTHONG et al., 2021). LI et al. (2010) demonstrated that synoviocyte proliferation in adjuvant arthritis rats was apparently suppressed after hesperidin treatment, which was accompanied by not only decreased levels of tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-1 beta (1β) from synoviocytes, but also increased IL-10 levels. Additionally, YEH et al. (2007) reported that hesperidin has an anti-inflammatory effect by decreasing the expression of proinflammatory cytokines (TNF-α, IL-1β, IL-6) and chemokines in lipopolysaccharide-induced lung inflammation. In the light of these scientific studies (YEH et al., 2007; LI et al., 2010; PRASATTHONG et al., 2021), it is thought that the administration of hesperidin may be beneficial in the prevention of metabolic syndrome in which inflammatory reactions play an essential role. Moreover, pharmaceutical therapy in metabolic syndrome is aimed at treating the individual components of metabolic syndrome, including antihypertensives, statins, and metformin, in other words, there is no single drug therapy for metabolic syndrome (ROCHLANI et al., 2017). Thus, nowadays the use of natural bioactive compounds is trending as an alternative method for the treatment and management of metabolic syndrome (MOSQUEDA-SOLÍS et al., 2020). The main aim of the present study was to evaluate whether the administration of hesperidin-added rat food improves inflammation and associated metabolic syndrome in fructose-fed rats, by analyzing both serum and liver TNF-α, IL-1β, IL-6, IL-10, and transforming growth factor-beta (TGF-β) levels.

Materials and methods

Animals and experimental design. Twenty-four, six-week-old male Wistar albino rats with an initial body weight of 118-140 grams, provided by Gazi University Laboratory Animals Breeding and Experimental Researches Center, were used in this study. The present study protocol was approved by Gazi University Animal Experiments Local Ethics Committee (G.Ü.ET-16.064, 13.07.2016), and the experimental studies were conducted in accordance with the ethical rules. Metabolic syndrome was induced by feeding the rats a 10% fructose-enriched diet for 10 weeks according to the method described by BERNASCONI et al. (2013). The hesperidin dose in rats was supplemented according to the method reported by AKIYAMA et al. (2010). The rats were randomly assigned to one of the four following groups (n=6 per group): Control (C), hesperidin (H), metabolic syndrome (MS) and metabolic syndrome + hesperidin (MS+H). The control group was fed *ad libitum* with a standard chow diet and drinking water for 10 weeks. The H group was fed *ad libitum* with a specially prepared hesperidin supplemented standard chow diet (1%, 10 g/kg feed) and drinking water for 10 weeks. The MS group was fed *ad libitum* with a standard chow diet and 10 % fructose added to drinking water for 10 weeks. The MS+H group was fed *ad libitum* with a specially prepared hesperidin supplemented standard chow diet (1%, 10 g/kg feed) + 10% fructose added to drinking water for 10 weeks. The body weights of the rats were recorded once weekly. At the end of the study, anesthesia was generated using a cocktail made of xylazine (5 mg/kg, i.m.) and ketamine hydrochloride (45 mg/kg, i.m.). Before performing necropsies, blood was taken by cardiac puncture and the liver tissues were removed. The blood was centrifuged at 3000 rpm for 10 minutes at +4°C, the serum was removed and stored at -20°C, and the liver tissues were stored at -80°C until analyses.

Liver tissue preparation. All the liver tissues were individually homogenized in 10 ml sterile phosphate buffer (pH: 7.4) with an ultrasonic homogenizer in cooled tubes with ice. The homogenates were immediately centrifuged at 2000 rpm for 15 minutes at +4°C. The supernatants were separated and centrifuged at 22.000 g for 30 minutes at +4°C. Then, new supernatants were filtered through 0.45 µ filter paper and centrifuged at 22.000 g for 30 minutes at +4°C. The last supernatants were aliquoted and stored at −80°C until analyses.

Measurement of serum biochemical parameters. Serum glucose, insulin, albumin, triglycerides, cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transferase (GGT) were analyzed with a commercially available kit (BioSystems S.A., Barcelona, Spain) using photocolorimetry with an Analyzer A15 spectrophotometer (BioSystems S.A., Barcelona, Spain). Levels of blood insulin in fasted animals were assessed using a rat insulin enzyme-linked immunosorbent assay kit (A05105, Bertin Bioreagent, France). The homeostasis model assessment of basal insulin resistance (HOMA-IR) was calculated as the product of the fasting glucose level (mg/dL) and fasting insulin level (ng/ml) divided by a constant, 22.5 (MATTHEWS et al., 1985).

Determination of cytokines. Interleukin 1 beta (PicoKine™ ELISA, MBS175941), IL-6 (PicoKine™ ELISA, MBS355410), IL-10 (PicoKine™ ELISA, MBS824656), TNF-α (PicoKine™ ELISA, MBS267737), and TGF-β (PicoKine™ ELISA, MBS260302) were analyzed in serum and liver tissue with commercial kits using enzyme-linked immunosorbent assay (ELISA). All parameters were studied in duplicate. The methods recommended by the manufacturers were applied in the analyses, using commercial ELISA test kits designed specifically for rat cytokines. For each parameter, the absorbance of the color formed on the microplate was evaluated in the microplate reader (Infinite F50, Tecan Austria GmbH, Grödig, Austria), and the results were calculated from the standard curves.

Statistical analysis. The Windows Statistical Package for the Social Sciences 22.0 (IBM SPSS 22.0, USA) program was used to perform the statistical analysis. Comparison of multiple groups

was determined by analysis of variance (ANOVA) and the post-hoc Duncan test for parameters including triglyceride, CHOL, HDL, AST, ALT, GGT, IL-1β, IL-10, and TGF-β in serum and liver TNF-α, IL-1β, IL-6, and TGF-β. The data was checked for normality with the Shapiro Wilk Test and for homogeneity of variance with the Levene's Test. The Mann–Whitney *U* was the non-parametric test used to serum glucose, insulin, HOMA-IR, albumin, LDL, TNF-α, IL-6 and liver IL-10 as the non-parametric equivalent of the independent samples *t* test. Differences were considered significant at $P<0.05$. All variables were expressed as the mean ± standard error (SE).

Results

In the present study, fructose was given by means of a 10% fructose solution prepared daily in tap water for 10 weeks to the male Wistar albino rats in the metabolic syndrome (MS and MS+H) groups. There was an important difference in body weight gain between the C and metabolic syndrome groups (MS and MS+H) after 10 weeks (Fig. 1, Table 1). However, no significant body weight gain was observed in the H group when compared to the C group. A relationship was found between increased body weight and metabolic syndrome (Fig. 1, Table 1).

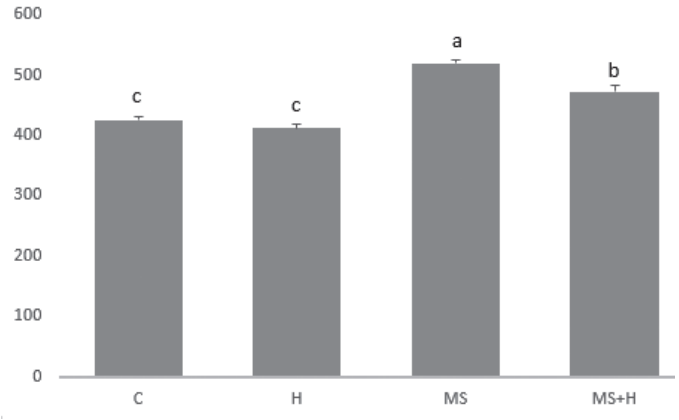

Fig. 1. Rat body weights in groups at the end of the study

C=control; H=hesperidin; MS=metabolic syndrome; MS+H=metabolic syndrome+hesperidin. The data are presented as the mean ± SE (n=6). Bars with different lowercase letters represent statistically significant differences ($P<0.001$, Kruskal-Wallis test and Mann Whitney U test

Table 1. The initial and final body weights of the rats

Groups	Initial body weight of the rats	Final body weight of the rats
C	128.67±2.89^{b}	425.17±5.20^{a,*}
H	127.00±2.67^{b}	411.17±6.35^{a,**}
MS	124.83±2.12^{b}	519.33±5.58^{a,**}
MS+H	129.00±3.20^{b}	472.17±10.00^{a,*}

The data are presented as the mean ± SE (n=6). C=control; H=hesperidin; MS= metabolic syndrome; MS+H= metabolic syndrome+hesperidin. Different lower case letters represent statistically significant differences between any two groups *($P<0.05$) Wilcoxon test; **($P<0.001$) Paired-Samples t-test

At the end of the study, fructose-induced hyperglycemia, hyperinsulinemia, insulin resistance, hypercholesteremia, hypertriglyceridemia, and also significant increases in body weight were observed, including metabolic syndrome criteria, compared with the C group (Table 2).

Data regarding the levels of serum biochemical parameters are shown in Table 2. Serum glucose, insulin, and HOMA-IR values were significantly higher in MS rats when compared to C, H and MS+H rats. It was determined that serum triglyceride, total cholesterol and LDL levels and the activities of ALT, AST and GGT were significantly higher ($P<0.001$ for each comparison in serum) and HDL levels significantly lower ($P<0.001$) in the MS group compared to the others (C, H, and MS+H group). Albumin levels were significantly lower in the MS group compared to the C group ($P<0.05$).

The serum and liver IL-1β, IL-6, IL-10, TNF-α and TGF-β concentrations in the groups are presented in Table 3. The metabolic syndrome group had significantly higher concentrations of TNF-α, IL-1β, and IL-6, and lower concentrations of IL-10 and TGF-β than the others (C, H, and MS+H group) ($P<0.001$ for each comparison in the serum and liver, Table 3).

Table 2. Serum biochemical parameters of the groups

Parameters	C (n=6)	H (n=6)	MS (n=6)	MS+H (n=6)	Sig.
Glucose (mg/dL)	94.33±2.26^{c}	91.17±2.04^{c}	202.67±6.89^{a}	131.17±6.04^{b}	P<0.001
Insulin (ng/mL)	1.38±0.11^{c}	1.27±0.07^{c}	5.02±0.48^{a}	2.55±0.17^{b}	P<0.001
HOMA-IR index	5.85±0.60^{c}	5.17±0.38^{c}	45.92±5.94^{a}	15.08±1.66^{b}	P<0.001
Albumin (g/dL)	3.63±0.07^{a}	3.67±0.11^{ab}	3.12±0.11^{b}	3.50±0.15^{ab}	P<0.05
Triglyceride (mg/dL)	77.83±6.65^{c}	75.17±6.42^{c}	169.67±6,65^{a}	105.00±5,15^{b}	P<0.001
CHOL (mg/dL)	68.17±3.53^{c}	65.00±2.94^{c}	179.33±5.21^{a}	99.67±4.22^{b}	P<0.001
HDL (mg/dL)	43.33±1.96^{a}	45.67±1.61^{a}	27.83±2.29^{c}	36.00±1.71^{b}	P<0.001
LDL (mg/dL)	18.17±1.40^{c}	16.33±1.50^{c}	89.50±5.99^{a}	33.17±3.05^{b}	P<0.001
AST (U/L)	78.17±3.62^{c}	81.17±2.59^{c}	130.83±7.12^{a}	98.33±3.52^{b}	P<0.001
ALT (U/L)	64.33±2.96^{c}	67.50±2.77^{c}	102.67±4.20^{a}	88.17±2.86^{b}	P<0.001
GGT (U/L)	28.33±1.86^{c}	32.00±2.02^{c}	62.00±1.98^{a}	43.67±1.91^{b}	P<0.001

C=control; H=hesperidin; MS=metabolic syndrome; MS+H=metabolic syndrome+hesperidin. Means within rows without common superscripts differ significantly ($P<0.05$, $P<0.001$)

Table 3. The serum and liver concentrations of proinflammatory and anti-inflammatory cytokine of the groups

	Cytokine	C (n=6)	H (n=6)	MS (n=6)	MS+H (n=6)
SERUM	TNF-α (ng/mL)	6.23±0.53^{b}	5.93±0.24^{b}	15.13±1.52^{a}	11.25±1.32^{a}
	IL-1β (ng/mL)	3.15±0.39^{c}	3.47±0.17^{c}	7.25±0.25^{a}	4.90±0.32^{b}
	IL-6 (ng/mL)	2.05±0.16^{c}	1.88±0.21^{c}	5.63±1.50^{a}	3.53±0.16^{b}
	IL-10 (ng/mL)	5.43±0.28^{a}	5.65±0.19^{a}	2.07±0.21^{c}	4.23±0.23^{b}
	TGF-β (ng/mL)	18.06±1.07^{a}	19.03±1.36^{a}	9.53±1.06^{c}	12.55±1.67^{b}
LIVER	TNF-α (ng/g tissue)	12.28±0.77^{c}	11.02±0.86^{c}	27.83±2.36^{a}	18.43±2.07^{b}
	IL-1β (ng/g tissue)	11.83±1.01^{c}	10.43±1.26^{c}	27.18±2.38^{a}	18.08±1.43^{b}
	IL-6 (ng/g tissue)	10.08±1.17^{c}	9.42±1.23^{c}	19.18±1.23^{a}	15.08±1.31^{b}
	IL-10 (ng/g tissue)	19.53±1.43^{ab}	22.00±1.85^{a}	7.72±0.72^{c}	14.00±0.38^{b}
	TGF-β (ng/g tissue)	60.27±3.06^{a}	62.67±4.00^{a}	36.12±3.60^{c}	47.82±2.12^{b}

C=control; H=hesperidin; MS=metabolic syndrome; MS+H=metabolic syndrome+hesperidin. Means within rows without common superscripts differ significantly ($P<0.001$)

Discussion

Metabolic syndrome represents a cluster of clinical and biochemical abnormalities such as obesity, impaired blood lipid and glycemic parameters, insulin resistance, and atherogenic dyslipidemia (ROCHLANI et al., 2017; ZAFAR et al., 2019). In the present study, the effect of hesperidin on the inflammatory response in a model of inducing metabolic syndrome was investigated. It was determined that the concentrations of proinflammatory cytokines TNF-α, IL-1β, and IL-6 increased significantly in the serum and liver tissues of rats exposed to high-dose fructose exposure, to induce metabolic syndrome, but hesperidin treatment suppressed this increase. In addition to this, it was understood that hesperidin administration increased the low IL-10 and TGF-β concentrations caused by metabolic syndrome. KARAM et al. (2017) reported that hyperlipidemia is associated with inflammation. However, FAN et al. (2019) stated that hypertriglyceridemia is linked to the reduced HDL through the generation of LDL which is related to metabolic syndrome characteristics, independently of inflammation and obesity. Consistent with a prior study (FAN et al., 2019), it was found that serum triglyceride, total cholesterol, LDL, and proinflammatory cytokines levels were significantly higher, and HDL and anti-inflammatory cytokines levels significantly lower in MS rats than in the others. The results demonstrated metabolic syndrome is related to inflammation, so this study may support the view of KARAM et al. (2017) on this issue.

Metabolic syndrome development is associated with a chronic state of inflammation, characterized by abnormal proinflammatory cytokine production (MONSERRAT-MESQUIDA et al., 2020; ABDELAZEEM et al., 2021). Obesity is related to induced adipocyte secretion of factors that decrease insulin-mediated glucose uptakes, such as free fatty acids and proinflammatory cytokines, including TNF-α, IL-1β, and IL-6 (HOTAMISLIGIL, 2006). Interleukin-10 has been shown to exert essential protective effects on the development of atherosclerotic lesions in experimental animals (OSLUND et al., 1999). It is known that TNF-α is an essential link between inflammation, obesity and insulin resistance (PHILLIPS and PERRY, 2013); IL-1β promotes hepatic steatosis by stimulating cholesterol accumulation, triglycerides, and formation of lipid droplets, which decreases insulin-stimulated glucose uptake and lipogenesis, and regulates inflammation, hepatic insulin resistance, and fibrosis (MIURA et al., 2010; DONATH and SHOELSON, 2011); IL-6 impairs insulin signaling and action (MARTIN-CORDERO et al., 2011) and possesses different influences that create a dual role in modulating insulin sensitivity, acting as both an enhancer and inhibitor of insulin action (SETHI and HOTAMISLIGIL, 1999). Thus, it may be important to determine the levels of these cytokines in metabolic syndrome studies. TIMAR et al. (2014) suggested that metabolic syndrome is associated with higher insulin and increased insulin resistance. Moreover, they measured high TNF-α, IL-6 and low anti-inflammatory cytokines in patients with metabolic syndrome. CHOI et al. (2007) found that individuals with metabolic syndrome demonstrate lower serum IL-10 levels and higher serum IL-6 levels compared to those without metabolic syndrome. SALMENNIEMI et al. (2004) reported that serum IL-1β levels are increased in metabolic syndrome in humans. Furthermore, metabolic syndrome promotes insulin resistance and causes increased insulin requirements, with subsequent deterioration of glycemic control and weight gain (TILG and MOSCHEN, 2008). As it is stated in the literature, in the present study, it was determined that with increased glucose, insulin and HOMA-IR index levels and weight gain in rats, obesity occurred in the MS group, and also increases in serum and liver TNF-α, IL-1β, and IL-6 levels. The findings of the current study were comparable with similar results in humans. As in this study, PADIYA et al. (2011) reported an increase in the levels of blood glucose, insulin triglycerides, and cholesterol after 8 weeks of high fructose feeding in a rat metabolic syndrome model. IL-1β inhibition was reported to attenuate hepatic steatosis and liver damage, ameliorate atherosclerosis, and lower glycemia (KIRII et al., 2003; OSBORN et al., 2008; TILG et al., 2016). The current study demonstrates for

the first time that rats with metabolic syndrome provocation and hesperidin treatment had elevated anti-inflammatory cytokine (IL-10 and TGF-β) concentrations and decreased proinflammatory cytokine (TNF-α, IL-1β, and IL-6) concentrations, and less weight compared to rats with metabolic syndrome. In the present study, hesperidin also normalized the increased serum values of triglyceride, total cholesterol, LDL, ALT, AST, and GGT, and decreased HDL values after fructose feeding. Moreover, it is thought that hesperidin may possess a protective and therapeutic effect for the liver against pathological states.

Conclusions

The findings of the study revealed that hesperidin exerted an anti-inflammatory effect by suppressing the serum and liver proinflammatory cytokine response and stimulating the anti-inflammatory cytokine response in a rat metabolic syndrome model. It is predicted that the results of this study, which strengthens the hypothesis that hesperidin can potentially be used in alleviating inflammation in metabolic syndrome, will contribute to the studies to be conducted on inflammation that develops in metabolic syndrome, and to the treatment of metabolic syndrome. Thus, further study is necessary to determine whether hesperidin may help in the management of metabolic syndrome in humans.

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SAŽETAK

Kod metaboličkog sindroma aktivirani upalni signalni putevi pokreću otpuštanje proupalnih citokina. Pri liječenju odnosno upravljanju metaboličkim sindromom, danas je kao alternativna metoda sve češća upotreba prirodnih bioaktivnih sastojaka. Cilj je istraživanja bio procijeniti moguće učinke hesperidina kod modela štakora s metaboličkim sindromom. Analizirani su proupalni i protuupalni citokini u serumu i jetri. Štakori su podijeljeni u četiri skupine: kontrolna skupina (štakori hranjeni standardnom hranom za žvakanje i vodom *ad libitum*), skupina hesperidin (štakori hranjeni standardnom hranom za žvakanje kojoj je dodan hesperidin 1%, 10 g/kg hrane i voda *ad libitum*) skupina s metaboličkim sindromom (štakori hranjeni standardnom hranom za žvakanje s 10% fruktoze dodane u vodu za piće) i skupina s metaboličkim sindromom i hesperidinom (štakori hranjeni standardnom hranom za žvakanje kojoj je dodan hesperidin 1%, 10 g/kg s 10% fruktoze u vodi za piće). Štakori su eutanazirani uz anesteziju ketaminom i ksilazinom, te su im uzeti uzorci krvi i tkiva jetre. Testom ELISA, u serumu i jetri, izmjereni su faktor tumorske nekroze-alfa, interleukin -1 beta, interleukin-6, interleukin-10 i transformacijski faktor rasta-beta. U skupini s metaboličkim sindromom u usporedbi s kontrolnom skupinom pronađene su povišene vrijednosti faktora tumorske nekroze-alfa, interleukina 1-beta i interlekina-6 te snižene vrijednosti interleukina-10 i transformacijskog faktora rasta-beta. Osim toga, u skupini s metaboličkim sindromom i hesperidinom u odnosu na skupinu s metabaličkim sindromom pronađene su snižene vrijednosti interleukina -1 beta i interleukina-6 te povišene vrijednosti interleukina-10 i transformacijskog faktora rasta-beta. Zaključeno je da je u modelu štakora s metaboličkim sindromom hesperidin potisnuo odgovor proupalnih citokina u serumu i jetri te potaknuo protuupalni odgovor citokina.

Ključne riječi: citokini; hesperidin; sindrom inzulinske rezistencije; jetra; štakor