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Quercetin supplementation in metabolic syndrome: nutrigenetic interactions with the *Zbtb16* gene variant in rodent models

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Abstract

Background Quercetin is a promising phytochemical in treating abnormalities associated with metabolic syndrome (MetS). This study aimed to explore the morphometric, metabolic, transcriptomic, and nutrigenetic responses to quercetin supplementation using two genetically distinct MetS models that only differ in the variant of the MetS-related *Zbtb16* gene (Zinc Finger And BTB Domain Containing 16).

Results Quercetin supplementation led to a significant reduction in the relative weight of retroperitoneal adipose tissue in both investigated strains. A decrease in visceral (epididymal) fat mass, accompanied by an increase in brown fat mass after quercetin treatment, was observed exclusively in the SHR strain. While the levels of serum triglycerides decreased within both strains, the free fatty acids levels decreased in SHR-Zbtb16-Q rats only. The total serum cholesterol levels were not affected by quercetin in either of the two tested strains. While there were no significant changes in brown adipose tissue transcriptome, quercetin supplementation led to a pronounced gene expression shift in white retroperitoneal adipose tissue, particularly in SHR-Zbtb16-Q.

Conclusion Quercetin administration ameliorates certain MetS-related features; however, the efficacy of the treatment exhibits subtle variations depending on the specific variant of the *Zbtb16* gene.

Keywords Metabolic syndrome, Quercetin, Rats, ZBTB16, Cholesterol, Retroperitoneal fat

Background

Metabolic syndrome (MetS) is a clustering of cardiometabolic abnormalities that include obesity, impaired glucose metabolism, hypertension, and dyslipidemia [1, 2]. The syndrome is associated with a heightened risk of chronic and potentially life-threatening conditions, such as cardiovascular disease, type 2 diabetes, or certain types of cancer [3, 4]. Although the genesis of MetS is multifaceted, involving genetic and environmental factors, a comprehensive understanding of its etiology remains elusive. Unhealthy lifestyle patterns, including poor nutrition and sedentarism seem to play a fundamental role in its development as they might lead to weight gain and obesity [2,

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5, 6]. Excessive accumulation of adipose tissue, especially inside the abdominal cavity (visceral adipose tissue) and its associated endocrine mediators have been strongly associated with the pathogenesis of metabolic disorders constituting MetS [5–7]. However, other pathogenic factors, such as insulin resistance, oxidative stress, systemic inflammation, and/or mitochondrial dysfunction, might also be potentially involved in the pathogenesis of the syndrome [5, 8, 9].

Due to its increasing prevalence worldwide, MetS has become a main public health concern as it is associated with substantial health care costs [10]. Early diagnosis is pivotal in managing the risk factors associated with MetS development, however the complexity of the syndrome presents a formidable obstacle in finding effective treatment strategies. Current pharmacotherapy primarily addresses individual components of MetS, such as antihypertensive, hypolipidemic, and antidiabetic drugs. To our knowledge, a multifunctional drug capable of concurrently addressing all the pathological aspects of MetS is not currently available [11].

Quercetin is a naturally occurring polyphenolic compound found in various fruits and vegetables, such as onions, broccoli, tomatoes, apples, grapes, and berries [12]. Its beneficial effect on human health is well documented and includes anti-obesity, anti-hypertensive, anti-diabetic, anti-inflammatory and hypolipidemic properties [13–15]. While substantial evidence underscores quercetin's potential as a powerful therapeutic agent for addressing various components of MetS, limited information exists concerning the extent to which these effects depend on specific genetic backgrounds [16, 17].

The *Zbtb16* gene (Zinc Finger And BTB Domain Containing 16) encodes a transcription factor involved in regulating various cellular processes, such as cell proliferation, apoptosis, differentiation, stem cell maintenance, and organ development, acting as a master regulator [18, 19]. In recent years, *Zbtb16* has emerged as a crucial candidate gene in the development of MetS and has been linked to all its features [20]. Our research, along with that of others, has shown that variants of the *Zbtb16* gene influence the predisposition to MetS traits, including adipogenesis, insulin sensitivity, and lipid levels, in both humans and rodent models [20–22]. Additionally, *Zbtb16* has been reported to orchestrate hepatic lipid and glucose homeostasis [23, 24].

The spontaneously hypertensive rat (SHR) is a highly inbred model of MetS that exhibits hypertension, dyslipidemia, insulin resistance, and a predisposition to left ventricular hypertrophy and myocardial fibrosis. However, it is generally not considered obese [25]. We have previously shown that a congenic SHR-Zbtb16 strain, differing from the SHR in a single gene – *Zbtb16* – displays distinct profile in some of the MetS features - reduced white adipose tissue depots or lower fasting insulin [26] when fed a standard diet. Compared to its progenitor strain SHR, the SHR-Zbtb16 strain exhibits worse glucose tolerance, reduced insulin sensitivity in skeletal muscle, and higher serum triglycerides levels when administrated a high-sucrose diet [27]. In the present study, we used two inbred rodent models, differing only in their *Zbtb16* gene variant, to determine the effect of chronic oral quercetin supplementation on MetS-associated metabolic parameters as well as the transcriptomic profiles of two types of adipose tissue and potential nutrigenetic interactions between quercetin and the *Zbtb16* gene.

Methods

Rat strains

The spontaneously hypertensive rat (SHR/OlaIpcv, Rat Genome Database [28] (RGD) ID 631848; SHR hereafter), a commonly used model of essential hypertension, and a single congenic rat strain SHR-Lx.PD5$^{PD-Zbtb16}$ (hereafter referred to as SHR-Zbtb16) were used in this study due to their known metabolic abnormalities and sensitivity to dietary manipulation [26, 29]. The SHR-Zbtb16 strain carries the *Zbtb16* gene, originating from the polydactylous rat (PD/Cub, RGD ID 728161), on the SHR genomic background. Consequently, the two strains differ solely in the variant *Zbtb16* gene. The derivation of the strain and its genomic characterization was described previously [30]. Both strains are highly inbred and maintained by brother x sister mating at the Institute of Biology and Medical Genetics.

Experimental protocol

Adult male rats of the SHR and SHR-Zbtb16 strains were held under temperature- (23 °C) and humidity- (55%) controlled conditions on 12-h light/12-h dark cycle and fed a laboratory chow diet (STD, ssniff RZ, ssniff Spezialdiäten GmbH, Soest, Germany). At all times, the animals had *ad libitum* access to food and water. At 12 months of age, rats within each strain were randomly divided into two groups (n=5–6/group): a control group fed a high-sucrose diet (HSD, proteins (19.6 cal%), fat (10.4 cal%), carbohydrates (sucrose, 70 cal%); SHR, SHR-Zbtb16 rats), prepared by the Institute for Clinical and Experimental Medicine, Prague, Czech Republic) [31]; and an experimental group fed a HSD fortified with quercetin (10 g/kg food, Sigma-Aldrich; SHR-Q, SHR-Zbtb16-Q rats). The quercetin dosage was chosen based on previous studies [32, 33]. Food and liquid intake were followed daily in all groups.

After two weeks of the experiment, blood samples were drawn after overnight fasting from the tail vein for the assessment of fasting metabolic parameters. Then, for the oral glucose tolerance test (OGTT), blood samples were

drawn from the tail vein at intervals of 30, 60, 90, 120 and 180 min following intragastric glucose administration (3 g/kg body weight, 30% aqueous solution) to conscious rats. Blood glucose concentrations over the 180-minute period were used to calculate the area under the curve. The rats were then sacrificed by decapitation under isoflurane anesthesia and the weights of the heart, liver, kidneys, adrenals, and brown, epididymal, and retroperitoneal adipose tissues were determined by using a digital analytical balance.

Biochemical parameters were determined as follows: serum total cholesterol and triglycerides concentrations using colorimetric kits from Erba Lachema (Czech Republic); free fatty acids using a kit from Roche Diagnostic (Germany); insulin with a rat insulin enzyme-linked immunosorbent assay kit (Mercodia, Uppsala, Sweden) and high-molecular weight (HMW) adiponectin using an ELISA kit (MyBioSource, USA). To determine triglycerides and cholesterol in the liver, samples were powdered under liquid nitrogen and extracted in chloroform/methanol. The mixture was centrifuged, the organic phase was removed and evaporated under N_2. The resulting pellet was dissolved in isopropyl alcohol, and the triglyceride content was determined by enzymatic assay (Erba-Lachema, Brno, Czech Republic). The same process was used to measure liver cholesterol.

Transcriptomic analysis

Total RNA was isolated from the brown and retroperitoneal adipose tissue (RNeasy Mini Kit, Qiagen, Hilden, Germany). The Agilent 2100 Bioanalyzer system (Agilent, Palo Alto, CA, USA) was employed to assess the quality and integrity of the extracted RNA. Only samples with an RNA Integrity Number (RIN) > 8.0 were considered suitable for further analysis. Microarray experiments were conducted using samples obtained from three different animals for each group and tissue type, utilizing the Rat Gene 2.1 ST Array Strip, i.e. total of 24 microarrays were processed. The Affymetrix GeneAtlas® system was utilized for the hybridization process, following the manufacturer's guidelines. Chip quality control was carried out using the Affymetrix Expression Console software (Affymetrix, Santa Clara, CA, USA), while data analysis was performed with the Partek Genomics Suite (Partek, St. Louis, MO, USA). After applying quality filters and normalizing data using the Robust Multichip Average (RMA) algorithm, differentially expressed probe sets were identified using factorial ANOVA with STRAIN and QUERCETIN as major factors, implemented in Partek Genomics Suite 7 (Partek, St. Louis, MO, USA). Only probe sets with a false discovery rate (FDR) < 0.05 and, at the same time, showing a > 1.2 fold or < −1.2 fold difference in expression between the compared groups, were subjected to further analyses. The filtered transcriptomic data underwent a standardized sequence of analyses, including hierarchical clustering, principal component analysis, gene ontology, gene set enrichment, upstream regulator analysis, mechanistic networks, causal network analysis, and downstream effects analysis, utilizing Partek Pathway, Ingenuity Pathway Analysis [34] and the enrichment analysis tool Enrichr and the enrichment analysis tool Enrichr [35].

RT-qPCR

To validate the gene expression data obtained by microarray, quantitative real-time PCR (RT-qPCR) was performed. The amount of 1 µg of total RNA was used to synthesize cDNA using oligo-dT primers and the SuperScript III reverse transcriptase (Invitrogen, Carlsbad, CA, USA). For validation, the following sets of TaqMan® probes (Thermofisher; Waltham, MA, USA) were used: *Ptprd* (Rn01454928_m1), *Acss2* (Rn01753668_m1), *Nnat* (Rn00822063_m1), *Acad11* (Rn01746580_m1), *Tgm2* (Rn00571440_m1), *Cyp7b1* (Rn01461862_m1), *Serpina12* (Rn01518409_m1), *Calml3* (Rn01487166_s1). RT-qPCR reactions were performed in triplicate with samples taken from three distinct animals for each group and tissue type using TaqMan Gene Expression Master Mix (Applied Biosystems), adhering to the manufacturer's protocol (Invitrogen, Carlsbad, CA, USA) and employing Applied Biosystems 7900HT Real-Time PCR System. Cycle threshold (Ct) values were normalized by using glyceraldehyde-3-phosphate dehydrogenase (*Gapdh*) (TaqMan® chemistry, Applied Biosystems) as standard. Relative quantification was performed using the using the $2^{-\Delta\Delta Ct}$ method [36], followed by factorial ANOVA with STRAIN and QUERCETIN as major factors, followed by post-hoc Fisher's test for comparison of the specific pairs of variables. P-value < 0.05 was considered significant.

Statistical analysis

All statistical analyses were carried out using Statistica (data analysis software system), version 14 (TIBCO Software Inc., Palo Alto, CA, USA). Morphometric and metabolic variables of the two rat strains were compared by factorial ANOVA with STRAIN and QUERCETIN (Q) as major factors, followed by post-hoc Fisher's test for comparison of the specific pairs of variables. P-value < 0.05 was considered significant.

Results

Morphometric and metabolic parameters

The effect of quercetin on morphometric and metabolic parameters in SHR, SHR-Q, SHR-Zbtb16 and SHR-Zbtb16-Q rats is summarized in Table 1. No differences in the water and food intake, as well as the daily dose of quercetin, were observed among the groups (Supplementary Fig. 1), however, the percentual change in the initial

Table 1 Effect of quercetin supplementation on morphometric and metabolic variables in SHR and SHR-Zbtb16 rats

Variables	SHR	SHR-Q	SHR-Zbtb16	SHR-Zbtb16-Q	P_{ANOVA}
Morphometric variables					
Initial body weight (g)	$393 \pm 8^{\chi}$	$383 \pm 8^{\chi}$	$387 \pm 7^{\chi}$	$352 \pm 7^{\alpha\beta}$	**S** (0.035), **Q** (0.015)
Final body weight (g)	$404 \pm 7^{\chi}$	$396 \pm 7^{\chi}$	$393 \pm 5^{\chi}$	$347 \pm 7^{\alpha\beta}$	**S** (0.001), **Q** (0.003), **SxQ** (0.024)
Heart (g/100 g b.wt.)	0.44 ± 0.02	0.43 ± 0.01	0.43 ± 0.01	0.41 ± 0.003	n.s.
Liver (g/100 g b.wt.)	$3.01 \pm 0.1^{\beta\chi}$	$3.44 \pm 0.05^{\beta}$	$3.01 \pm 0.08^{\alpha\chi}$	$3.50 \pm 0.06^{\beta}$	**Q** (13.10^{-6})
Kidneys (g/100 g b.wt.)	$0.80 \pm 0.01^{\alpha\beta\chi}$	0.75 ± 0.01	0.74 ± 0.01	0.72 ± 0.01	**S** (0.002), **Q** (0.004)
Adrenals (mg/100 b.wt.)	$12.85 \pm 0.48^{\chi}$	$13.12 \pm 1.16^{\chi}$	$13.35 \pm 0.28^{\chi}$	$16.57 \pm 0.49^{\alpha\beta}$	**S** (0.026), **Q** (0.045)
Metabolic variables					
Adiponectin (µg/ml)	0.42 ± 0.09	0.36 ± 0.05	0.46 ± 0.04	0.31 ± 0.03	n.s.

Variables are mean ± SEM, $n = 5/6$ for each group. The comparison using the post-hoc Fisher's least significant difference test of the two-way ANOVA for STRAIN (S) and QUERCETIN (Q) as major factors and their interaction SxQ are indicated as follows: α, significantly different compared to SHR-Q; β, significantly different compared to SHR-Zbzt16; χ, significantly different compared to SHR-Zbtb16-Q, $p < 0.05$. SHR and SHR-Zbtb16: control rats, SHR-Q and SHR-Zbtb16-Q: rats supplemented with quercetin. b.wt.: final body weight

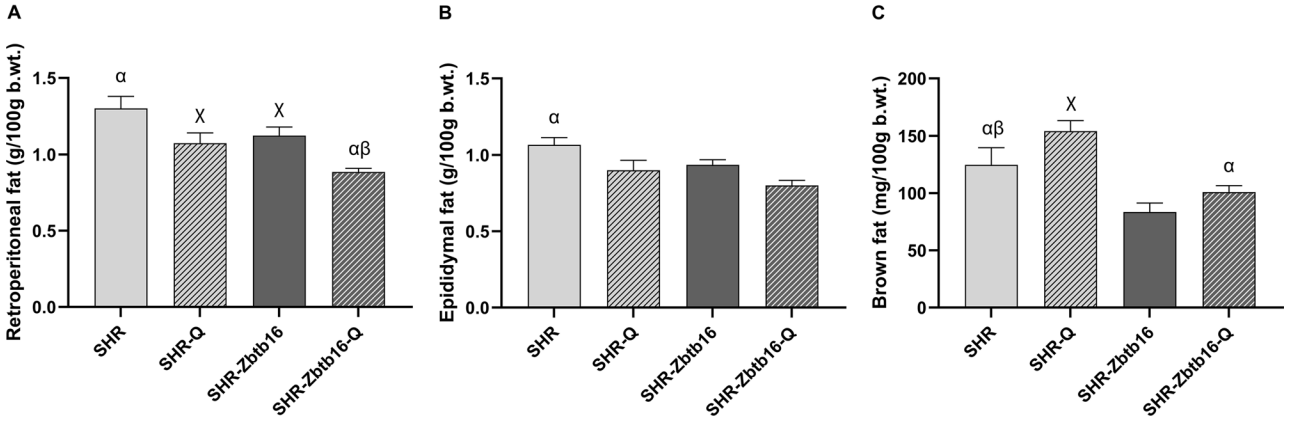

Fig. 1 Effect of quercetin supplementation on retroperitoneal (**A**), epididymal (**B**) and brown fat mass (**C**). Values are mean ± SEM, $n = 5/6$ for each group, post-hoc Fisher's least significant difference test of the two-way ANOVA for STRAIN and Q as major factors are indicated as follows: α, significantly different compared to SHR-Q; β, significantly different compared to SHR-Zbzt16; χ, significantly different compared to SHR-Zbtb16-Q. SHR and SHR-Zbtb16; control rats, SHR-Q and SHR-Zbtb16-Q; rats supplemented with quercetin. b.wt.: final body weight

body weight of SHR-Zbtb16-Q group was significantly smaller compared to the other tested groups (two-way ANOVA Strain x Quercetin interaction $p = 0.037$; Supplementary Fig. 2). The relative weight of liver increased following quercetin supplementation in both SHR-Q and SHR-Zbtb16-Q strains. The relative weight of kidneys was initially higher in the SHR strain compared to SHR-Zbtb16 rats; however, it decreased after quercetin treatment. In addition, quercetin significantly increased the adrenal tissue weight in the SHR-Zbtb16-Q rats compared to SHR-Zbtb16 and SHR-Q rats (Table 1).

Retroperitoneal and epididymal fat relative weights showed no differences between the control groups SHR and SHR-Zbtb16 strains. Quercetin significantly reduced retroperitoneal fat mass in both strains (see Fig. 1A); this effect was more pronounced in SHR-Zbtb16, resulting in significantly lower retroperitoneal fat weight in SHR-Zbtb16-Q compared to SHR-Q rats (Fig. 1B). The epididymal fat mass decreased only in SHR-Q rats (Fig. 1B). The relative weight of brown fat was higher in the control group of SHR strain compared to SHR-Zbtb16 and was further increased by quercetin supplementation. No change in brown fat mass within the SHR-Zbtb16 strain was detected after quercetin treatment (Fig. 1C).

With the exception of the SHR-Zbtb16 rats exhibiting lower blood glucose concentrations at 60th minute of the oral glucose tolerance test in compared to SHR rats, we detected no significant differences in glucose tolerance and serum insulin levels between the two strains' control groups (Fig. 2A). Fasting blood glucose levels were lower in the SHR-Zbtb16-Q rats compared to SHR-Q rats. During the oral glucose tolerance test, we observed lower blood glucose level at 30th minute in the SHR-Zbtb16-Q rats compared to SHR-Q rats. At the same timepoint, glucose levels increased within the SHR strain following quercetin supplementation (Fig. 2A). We observed a smaller glucose area under the curve and decreased fasting insulin levels in the SHR-Zbtb16-Q strain compared to SHR-Q strain after quercetin supplementation (Fig. 2B and C).

Adiponectin levels remained unchanged between the two tested strains and were not influenced by quercetin

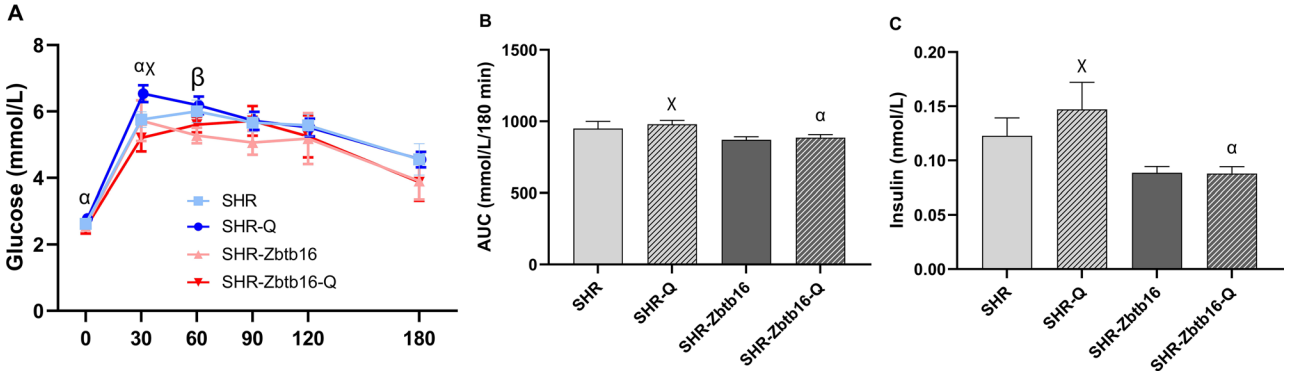

Fig. 2 Effect of quercetin supplementation on blood glucose levels during oral glucose tolerance test (**A**), area under the curve (AUC, **B**) and insulin (**C**) levels. Values are mean ± SEM, *n* = 5/6 for each group; SHR and SHR-Zbtb16; control rats, SHR-Q and SHR-Zbtb16-Q; rats supplemented with quercetin; post-hoc Fisher's least significant difference test of the two-way ANOVA for STRAIN and Q as major factors are indicated as follows: α represents differences in SHR-Q vs. SHR-Zbtb16-Q rats, χ represents differences in SHR vs. SHR-Q rats, β represents differences in SHR vs. SHR-Zbtb16 rats, α, significantly different compared to SHR-Q; β, significantly different compared to SHR-Zbzt16; χ, significantly different compared to SHR-Zbtb16-Q. SHR and SHR-Zbtb16; control rats, SHR-Q and SHR-Zbtb16-Q; rats supplemented with quercetin

administration. Total cholesterol levels were higher in control SHR-Zbtb16 rats compared to SHR rats, and although they were not impacted by quercetin in either of the two tested strains, the difference did not persist in the treated groups (Fig. 3A). Following quercetin treatment, triglyceride levels significantly decreased within both strains (Fig. 3B); however, free fatty acid levels only diminished in SHR-Zbtb16-Q rats (Fig. 3C). The triglyceride and cholesterol levels in the liver tissue were not significantly affected by quercetin (Fig. 3D, E).

Transcriptomic profiling of the brown adipose tissue

Although several brown adipose tissue transcripts were differentially expressed at a nominal level among the assessed groups, none of them passed the multiple testing correction. We confirmed this lack of difference in expression by quantitative polymerase chain reaction (qPCR) of the nominally most differentially expressed genes (Supplementary Table 3).

Transcriptomic profiling of the retroperitoneal white adipose tissue

The transcriptome profiles of the visceral adipose tissue in control groups were found to be similar (Table 2; all DEGs are listed in Supplementary Table 2 A); however, we identified 869 differentially expressed genes (DEGs) between groups treated with quercetin: 391 of those were significantly less expressed in SHR-Zbtb16-Q compared to SHR-Q and 478 genes showed relative overexpression in SHR-Zbtb16-Q (Supplementary Table 2B). The effect of quercetin administration was substantially more pronounced in SHR-Zbtb16 showing 240 DEGs (151 up- and 84 down-regulated by quercetin, respectively; Supplementary Table 2 C) compared to SHR with 40 DEGs (20 up- and 20 down-regulated by quercetin, respectively; Supplementary Table 2D). Only five of these genes were common between the two groups (Fig. 4). We were able to corroborate the microarray results with qPCR (Supplementary Table 3).

Numbers of significantly differentially expressed transcripts (FDR < 0.05; >1.2-fold-change for pair-wise comparisons) in visceral adipose tissue between SHR and SHR-Zbtb16 fed control diet (CTL) or diet supplemented with quercetin (Q) and between quercetin-treated and control rats within each strain (SHR; SHR-Zbtb16).

Apart from assessing the DEGs individually, we analyzed the transcriptome changes by several system-level approaches. The upstream regulator analysis takes into account all the observed expression changes and based on these datasets it determines and scores potential common upstream regulators and predict their activation or inhibition [29]. The upstream regulator analysis of quercetin effect in SHR-Q revealed six potential upstream regulators, none of which showed a clear prediction for their activation or inhibition, possibly due to the limited number of target downstream DEGs (Supplementary Table 4 A). In SHR-Zbtb16-Q, we identified eight upstream regulators based on the DEGs dataset. Based on the consistency of the pattern match between the up/down gene-regulation pattern, only two of the upstream regulators were predicted to be activated by quercetin administration in the retroperitoneal adipose tissue of SHR-Zbtb16 rats: the estrogen receptor alpha (Esr1) and forkhead box O1 (Foxo1; Fig. 5), as summarized in Supplementary Table 4B.

While we did not detect any enrichment of DEGs for quercetin effect in SHR or SHR-Zbtb16 by pathway enrichment analysis using the set of Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways. Ten significantly enriched pathways were revealed (adjusted significance level q < 0.05) based on DEGs of

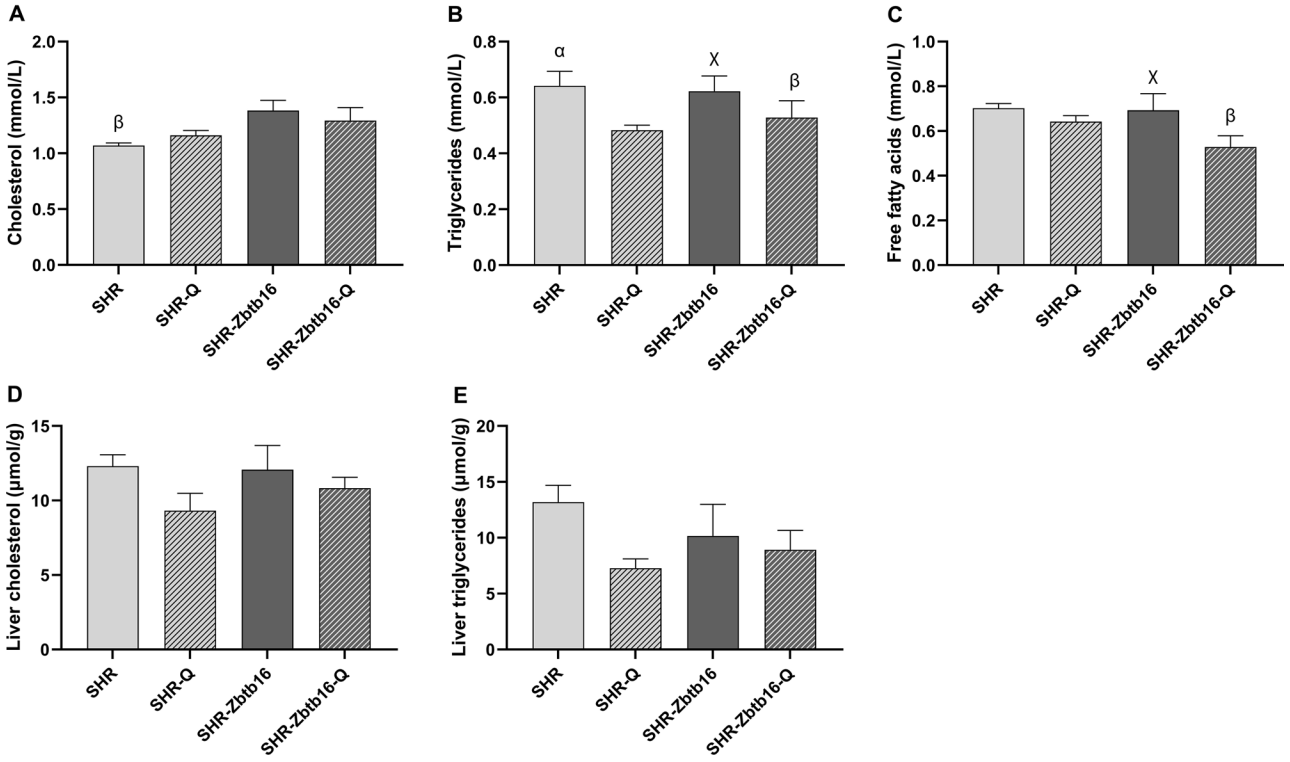

Fig. 3 Effect of quercetin supplementation on serum cholesterol (**A**), triglycerides (**B**), free fatty acids (**C**), liver cholesterol (**D**) and liver triglycerides (**E**). Values are mean ± SEM, *n* = 5/6 for each group, post-hoc Fisher's least significant difference test of the two-way ANOVA for STRAIN and Q as major factors are indicated as follows: α, significantly different compared to SHR-Q; β, significantly different compared to SHR-Zbzt16; χ, significantly different compared to SHR-Zbtb16-Q. SHR and SHR-Zbtb16; control rats, SHR-Q and SHR-Zbtb16-Q; rats supplemented with quercetin

Table 2 Numbers of differentially expressed transcripts in visceral adipose tissue

Comparison	upregulated	downregulated
CTL: SHR-Zbtb16 vs. SHR	1	1
Q: SHR-Zbtb16 vs. SHR	478	391
SHR: Q vs. CTL	20	20
SHR-Zbtb16: Q vs. CTL	151	89

the quercetin-treated groups (Fig. 6). The most enriched was oxidative phosphorylation (q=0.0047) mainly due to a concerted downregulation of multiple subunits of mitochondrial oxidative phosphorylation complexes in SHR-Zbtb16-Q: NADH: ubiquinone oxidoreductase (respiratory complex I), cytochrome c and ubiquinol-cytochrome c reductase (complex III), and cytochrome c oxidase (complex IV). The importance of oxidative phosphorylation in number of metabolic and neurological disorders is to certain extent reflected in the enrichment for the particular conditions (Supplementary Table 5).

Discussion

Metabolic syndrome (MetS) is a cluster of cardiometabolic risk factors for cardiovascular disease and type 2 diabetes [3]. Over the past few decades, MetS has become one of the main public health concerns, particularly due to its increasing prevalence among not only adults but also children and adolescents [37–39]. Quercetin, occurring naturally in various fruits and vegetables, belongs to one of the most abundant flavonoids in the human diet, with numerous studies documenting its health-promoting properties, including its potential to alleviate certain aspects of MetS [14, 16]. In this study, we examined the effects of quercetin on morphometric and metabolic parameters, as well as transcriptomic profiles, in two rat strains that differ solely in the variant of a MetS-related gene, the Zbtb16 gene.

Although the exact etiopathogenic factors of MetS remain to be fully elucidated, it is widely believed that an excess of abdominal (visceral) fat plays a pivotal role in the process, being the most prevalent feature in individuals with the syndrome [6, 7]. Numerous rodent studies showed that quercetin curtails weight gain induced by a high-fat diet and reduces total body fat mass, including visceral fat [40, 41]. Similar results upon quercetin treatment were observed in humans [42]. The pathways leading to adiposity involve adipocyte formation along with the triglyceride synthesis, both of which can be suppressed by quercetin through the regulation of gene expression and enzymatic activities involved in these processes [43–45]. The effects of polyphenols, including quercetin, are often highly dependent on the dose

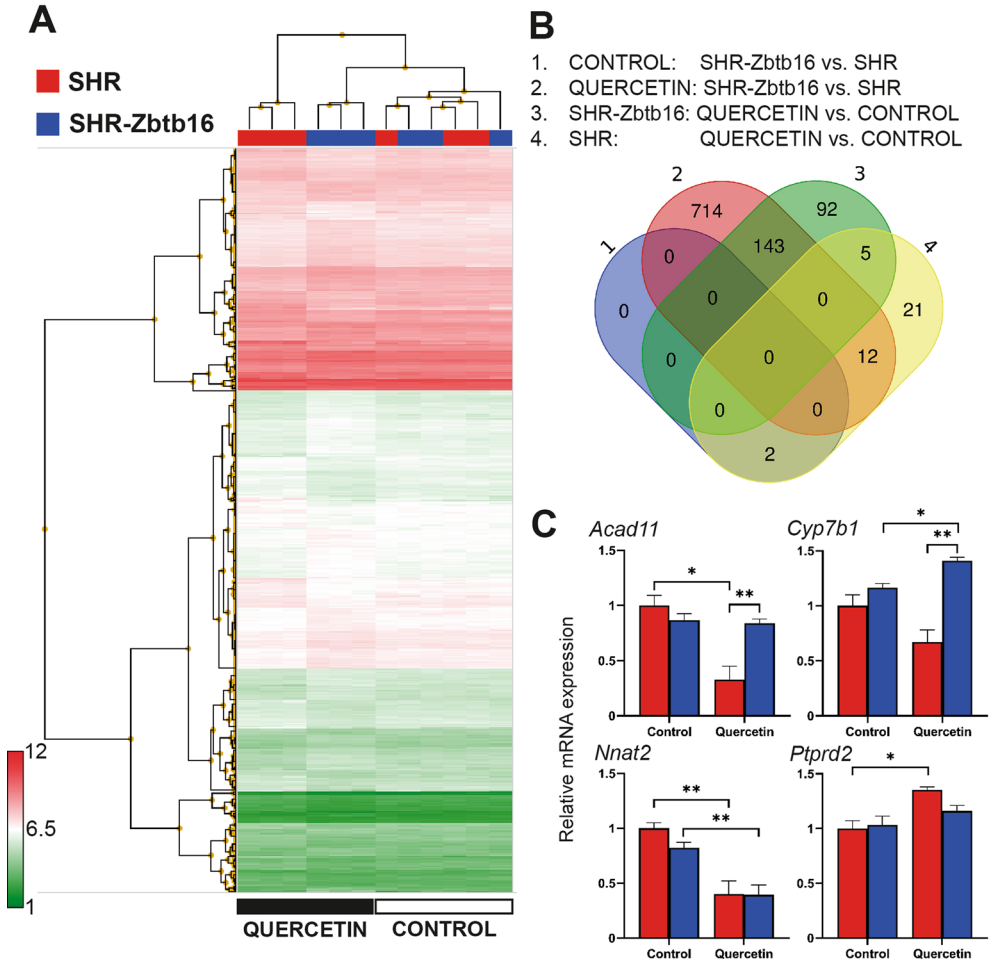

Fig. 4 Overview of gene expression profile in retroperitoneal adipose tissue of quercetin-treated and control SHR (red) and SHR-Zbtb16 (blue) rats. (**A**) Hierarchical clustering of significantly differentially expressed genes (DEGs). The clustering tree of the gene expression profiles is shown on the left, and the sample clustering tree appears at the top. The color scale indicates the relative gene expression levels, with red representing a high expression level and green, a low expression level. (**B**) Venn diagram depicting overlapping DEGs among the pair-wise comparisons. (**C**) The expression of selected genes (qPCR, all validated transcripts are shown in Supplementary Table 3). Values are presented as mean ± SEM ($n = 3$); p values < 0.05 were considered significant (*$p < 0.05$, **$p < 0.01$)

administered and the duration of treatment, with higher doses and prolonged administration typically resulting in more pronounced physiological effects. This dose-response relationship underscores the importance of optimizing dosage and administration protocols in both experimental and clinical settings to maximize the therapeutic benefits of quercetin [15, 46]. Recent literature had also proposed that the anti-obesity effect of quercetin might result from its ability to induce the browning of white adipose tissue, subsequently increasing energy expenditure [44, 45]. In line with these findings and our previous results in a distinct model of MetS, the PD/Cub rat strain [28], we observed that rats from both tested strains (SHR and SHR-Zbtb16) showed lower weights of retroperitoneal fat tissue following quercetin supplementation (Table 3). However, changes in the weights of the two other tested adipose tissues, namely decreased weight of epididymal fat and increased weight of brown fat were significantly affected only in the SHR strain, similarly to quercetin-treated Sprague-Dawley rats [47]. This suggests a possible nutrigenetic interaction between quercetin and *Zbtb16*, which is further supported by the disproportionate changes in retroperitoneal fat tissue transcriptomes of SHR vs. that of SHR-Zbtb16. There has been so far only limited evidence for genetic polymorphisms modulating the effects of quercetin intake, including stronger induction of ABCB1 in T/T homozygotes of its C3435T polymorphism [48] and a more prominent induction of CYP3A in CYP3A5*1/*1 and CYP3A5*1/*3 individuals [49]. While the exact mechanism of the proposed *Zbtb16*-quercetin interaction is not clear, the differentially enriched pathways suggest a complex set of interactions affecting facets of lipid metabolism, insulin signaling and oxidative phosphorylation, which is in line

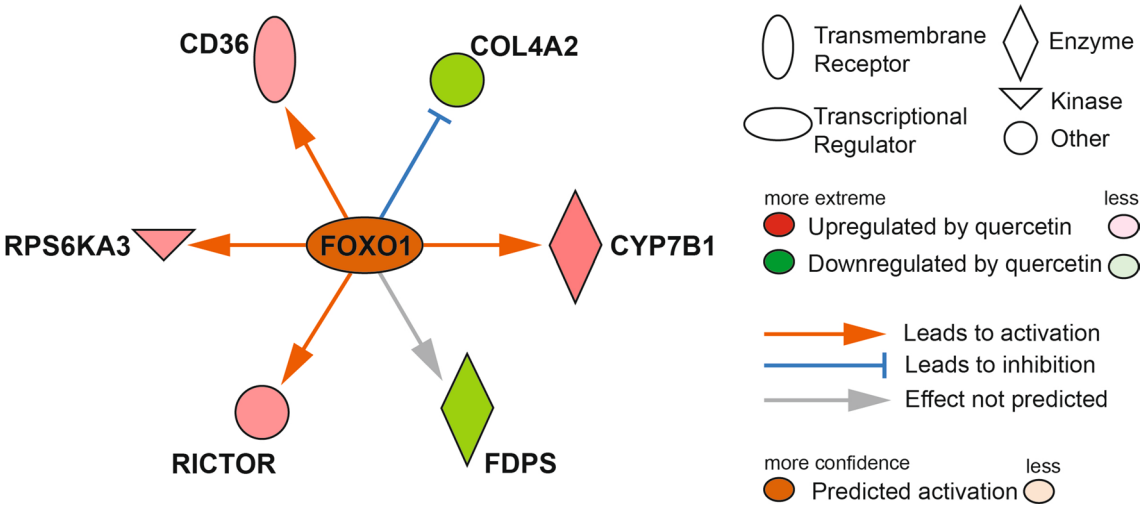

Fig. 5 Predicted significant quercetin-induced activation of *Foxo1* in retroperitoneal white adipose tissue of SHR-Zbtb16 rats based on the Upstream Regulator Analysis in the Ingenuity Pathway Analysis software [30]. The observed expression changes are shown in shades of red (upregulated by quercetin) and green (downregulated by quercetin)

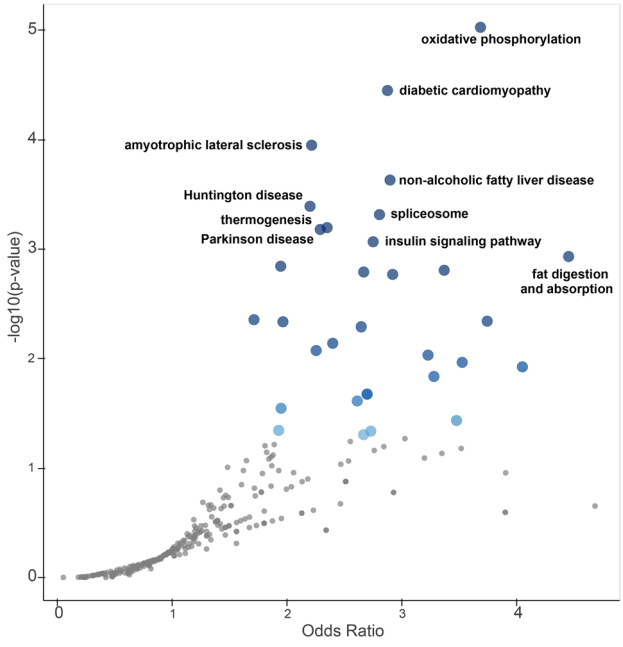

Fig. 6 Volcano plot of terms from the KEGG Pathway database. Each point represents a single term, plotted by the corresponding odds ratio (x-position) and -log10(p-value) (y-position) from the enrichment results of the gene set of differentially expressed genes in retroperitoneal adipose tissue between quercetin-treated SHR vs. SHR-Zbtb16 adult male rats. The larger and darker-colored the point, the more significantly enriched the input gene set is for the term. The name labels are provided only for the pathways passing the adjusted significance level ($q < 0.05$)

with previously described role of Zbtb16 as a pleiotropic node in metabolic syndrome [20]. One of the most downregulated gene in retroperitoneal fat by quercetin in both strains is neuronatin (Nnat), an endoplasmic reticulum membrane protein and a known regulator of whole-body metabolism and energy homeostasis [50, 51]. Nnat could thus be one of the major drivers of the effects of quercetin on the retroperitoneal adipose tissue common to both SHR and SHR-Zbtb16 rats. This was accompanied by strain-specific changes in expression profiles: in SHR, showing more significant adiposity reduction, one of the main upregulated genes was protein tyrosine phosphatase receptor type D (*Ptprd*) gene, whose increased expression was recently connected with restraining adipogenesis [52]; in SHR-Zbtb16, the main effects were consistent with predicted activation of upstream regulators Foxo1, a potent regulator of glucose and lipid metabolism in MetS-related tissues [53], and estrogen receptor Esr1, whose adipose tissue-specific knockout in males was shown to lead to obesity and insulin resistance [54, 55]. Furthermore, we detected an increased weight of the liver tissue in quercetin treated animals from both tested strains. Kuipers et al. obtained comparable results and hypothesized that this increase in liver mass may be attributable to greater triglyceride accumulation in the liver, resulting from decreased VLDL (Very-Low Density Lipoprotein) production [56, 57]. However, we found that the levels of triglyceride in the liver was not significantly increased by quercetin. In addition, in previous studies the weight of the liver tissue remained unaffected by quercetin or even decreased, as in our previous study [57, 58]. Further investigation is thus required to elucidate the effect of quercetin on liver tissue.

Mechanism of the anti-diabetic action of quercetin is pleiotropic and involves the inhibition of intestinal glucose absorption, stimulation of glucose uptake in tissues and organs via an insulin-dependent mechanism and/or alteration of liver enzymes involved in glucose metabolism [59–61]. In addition, quercetin treatment has been observed to increase insulin secretion and protect

Table 3 Quercetin effects in two metabolic syndrome models: SHR, PD, and SHR-Zbtb16 derived strain

Strain / Trait	WAT (RP)	WAT (EF)	BAT	GT	INS	TG	Liver TG	CH	Liver CH	FFA	Adpn
SHR	↓	↓	↑	—	—	↓	—	—	—	—	—
SHR-Zbtb16	↓	—	—	—	—	↓	—	—	—	↓	—
PD	↓	↓	—	—	—	↓	↓	—	—	↓	—

WAT: white adipose tissue; RP: retroperitoneal fat weight; EF: epididymal fat weight; BAT: brown adipose tissue; GT: glucose tolerance; INS: fasting insulin; TG: fasting triglycerides; CH: fasting cholesterol; FFA: fasting free fatty acids; Adpn: fasting adiponectin. The effects on PD strain are reported according to Kábelová et al. (2022); [33].

pancreatic β-cell against oxidative damage [62]. Furthermore, quercetin is also able to ameliorate diabetic retinopathy, nephropathy, and peripheral neuropathy, which are frequently encountered severe complications of diabetes [63, 64]. Regrettably, our study was unable to assess quercetin's anti-diabetic effect, as none of the models exhibited diabetic blood glucose levels. It should be noted that this study did not include an insulin tolerance test (ITT), which would have provided additional insights into insulin sensitivity. Including ITT in future studies will be important for a more comprehensive understanding of quercetin's effects on insulin dynamics.

Lipid profile abnormalities are an integral component of MetS and major risk factors for the development of cardiovascular diseases [65, 66]. While quercetin appears to exhibit a potential for normalizing blood lipid levels, the outcomes exhibit variability. Numerous studies have documented minimal to negligible improvements in lipid levels following quercetin administration, contributing to inconsistency in the observed effects [13, 67]. In this study, we observed that quercetin exerted no overall effect on total cholesterol levels but did significantly decrease triglycerides concentration. Furthermore, quercetin selectively decreased free fatty acids levels in the SHR-Zbtb16 strain. So far, several mechanisms leading to a decrease in the ma levels have been proposed, such as increased triglyceride (TG)-derived uptake of fatty acids by white adipose tissue as a consequence of browning and/or modulating gut microbiota [56, 68]. We may speculate that this genotype-specific effect is due to quercetin's concerted action on expression of multiple genes related to fatty acid turnover (including DEGs *Acad11*, *Abhd3*, *Acss2*, *Pla2g6*, *ACsm5*).

The limitations of this study include the use of only adult male rats of the two inbred strains, as the sex-specific genetic architecture of MetS and its components. Another limitation is the small groups of rats used in the experiment. Additionally, administering a single dose and regimen of quercetin to the model animals precludes the evaluation of dosage-dependent effects. The design of the experiment aimed to identify the subtle effects of short-term quercetin administration, thus necessitating the maximization of experimental and control group homogeneity.

Conclusion

In conclusion, individual features of the MetS, such as adiposity and blood lipid levels can be ameliorated by quercetin. However, the effect of the quercetin treatment might differ depending on the *Zbtb16* gene variant, suggesting the existence of a nutrigenetic interaction. In animals carrying the wild-type allele, quercetin appears to positively affect mainly the fat body content, whereas in the presence of the mutant allele, lipid profile improvements are more likely to result from quercetin treatment. Given the rising prevalence of MetS, dietary supplementation with either purified quercetin or quercetin-rich foods could potentially serve as an effective strategy for treating or even preventing the syndrome.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12263-024-00757-2.

Supplementary Material 1
Supplementary Material 2
Supplementary Material 3
Supplementary Material 4
Supplementary Material 5
Supplementary Material 6
Supplementary Material 7
Supplementary Material 8
Supplementary Material 9
Supplementary Material 10
Supplementary Material 11

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Author contributions
AK and OŠ designed research; AK, BC, HM, IM and MH conducted research; FL performed statistical analysis; AK and OŠ wrote the paper; AK had primary responsibility for the final content. All authors read and approved the final manuscript.

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Data availability
The generated and analyzed microarray data from this study can be accessed in the EMBL-EBI Biostudies repository (https://www.ebi.ac.uk/biostudies/) under accession number E-MTAB-11128.

Declarations

Ethics approval
All experiments adhered to the Animal Protection Law of the Czech Republic and the Directive 2010/63/EU of the European Parliament and of the Council and were approved by the Ethics Committee of the First Faculty of Medicine of the Charles University (Permit Number: MSMT-19427/2019-8).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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