

Original Article

The effect of quercetin on systemic inflammatory response and metabolism in rats under surgical and prolonged psychogenic stress

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Abstract

Prolonged psychogenic stress resembling post-traumatic stress disorder (PTSD), combined with surgical trauma, induces systemic inflammatory and metabolic disturbances. Quercetin, a natural polyphenol with antioxidant and anti-inflammatory properties, may attenuate these effects. This study evaluated the effects of water-soluble quercetin on systemic inflammatory response (SIR), carbohydrate metabolism, and lipid metabolism in rats subjected to surgical trauma following Single Prolonged Stress (SPS). Twenty-one adult male Wistar rats were allocated to three groups (n=7): control animals receiving polyvinylpyrrolidone (PVP), SPS plus surgical trauma animals receiving PVP, and SPS plus surgical trauma animals receiving a water-soluble quercetin–PVP complex equivalent to 20 mg/kg quercetin. Treatments were administered intragastrically for 7 days. Serum cortisol, ceruloplasmin, tumor necrosis factor- α (TNF- α), interleukins (IL-6 and IL-10), glucose, insulin, and lipid profile parameters were assessed using spectrophotometric and ELISA methods. Combined SPS and surgical trauma induced marked hypothalamic–pituitary–adrenal axis activation, systemic inflammation, insulin resistance, and dyslipidemia. Quercetin reduced serum cortisol and ceruloplasmin levels and markedly decreased TNF- α and IL-6 concentrations, while restoring the IL-10/IL-6 ratio toward control values. Quercetin also reduced blood glucose and HOMA-IR, although insulin levels remained elevated compared with controls. Lipid abnormalities were partially corrected, as evidenced by increased HDL cholesterol and decreased triglyceride and VLDL cholesterol levels, without significant changes in total or LDL cholesterol. Water-soluble quercetin attenuated stress- and surgery-induced inflammatory and metabolic disturbances, suggesting potential as an adjunctive strategy for reducing systemic inflammation and cardiometabolic alterations associated with combined psychological and surgical stress.

Keywords: quercetin, prolonged psychogenic stress, surgical trauma, systemic inflammatory response, insulin resistance, dyslipidaemia

Introduction

Recently, the full-scale armed aggression against Ukraine has led to a sharp increase in the incidence of psychological trauma among both military personnel and the civilian population [1]. This has, in turn, resulted in a significant rise in the prevalence of post-traumatic stress disorder (PTSD), which is now regarded not only as a psychiatric condition but also as a systemic disorder characterized by profound neuroendocrine,

immunoinflammatory, and metabolic disturbances. Current evidence suggests that PTSD is associated with the development of systemic inflammatory response (SIR), oxidative stress, and dysfunctions in carbohydrate and lipid metabolism, forming a phenotype that extends far beyond the traditional neuropsychiatric understanding of the disorder [2].

To replicate PTSD-like conditions in preclinical studies, the Single Prolonged Stress (SPS) model is widely used and is considered a validated experimental



paradigm [3]. Induction of SPS in rodents leads to characteristic behavioral, hormonal, and immune alterations that reflect key pathogenic mechanisms of PTSD, including dysregulation of the hypothalamic-pituitary-adrenal axis, impaired glucocorticoid feedback, and activation of proinflammatory signaling cascades [4, 5]. In addition, animals subjected to SPS exhibit deficits in fear extinction learning, a core clinical feature of PTSD in humans [6]. Despite the lack of formal diagnostic criteria for PTSD in animals, the SPS model remains a reliable tool for studying the molecular, immune, and metabolic aspects of stress-induced disorders [7].

Surgical trauma, a common consequence of combat injuries, can significantly potentiate the SIR, particularly in the presence of preceding psychoemotional stress. The combined impact of psychological burden and surgical intervention (surgical stress) results in excessive generation of reactive oxygen and nitrogen species, disruption of redox homeostasis, and mitochondrial dysfunction [8]. These alterations contribute to the development of SIR, characterized by sustained elevation of proinflammatory cytokines, acute-phase proteins, and connective tissue damage [9, 10], as well as disturbances in carbohydrate and lipid metabolism.

Redox-sensitive transcription factors, particularly NF- κ B (Nuclear factor kappa-light-chain-enhancer of activated B cells) and Nrf2 (Nuclear factor erythroid 2-related factor 2), play a crucial role in mediating stress-induced inflammatory and metabolic changes [11, 12]. Their imbalance sustains a “vicious cycle” of chronic inflammation and oxidative stress, underpinning the progression of neurodegenerative, cardiovascular, and metabolic diseases, as well as chronic inflammatory damage to internal organs [10].

Despite advances in the development of anti-inflammatory agents, most current therapeutic strategies focus on suppressing the terminal stages of the inflammatory response and do not target transcriptional regulation mechanisms. Moreover, synthetic modulators of transcription factors often present unfavorable safety profiles. In this context, natural polyphenols have garnered considerable attention as promising agents for pathogenetic correction due to their multi-target effects, good tolerability, and capacity to modulate multiple proinflammatory signaling pathways simultaneously [13–16].

Quercetin is one of the most extensively studied polyphenols, exhibiting potent antioxidant and anti-inflammatory properties, including NF- κ B inhibition, activation of Nrf2-dependent antioxidant mechanisms, and reduction in reactive oxygen species

production [17–19]. However, its clinical application has long been limited by poor water solubility and low bioavailability. The development of a water-soluble form of quercetin (Corvutin) has significantly improved the pharmacokinetic properties of the drug and its efficacy in models of SIR and oxidative stress [10].

Despite existing data on the anti-inflammatory and metabolic modulatory effects of quercetin, its impact under conditions of combined stress exposure, encompassing prior prolonged psychoemotional stress and subsequent surgical trauma, remains insufficiently investigated. Most available studies focus on isolated stress models, whereas the synergistic effects of multiple stressors may induce qualitatively distinct systemic changes. Therefore, a comprehensive investigation into the potential of quercetin to mitigate SIR and metabolic disturbances under such conditions is warranted.

The aim of this study was to evaluate the effect of quercetin on markers of systemic inflammatory response, as well as carbohydrate and lipid metabolism in rats subjected to surgical trauma following prolonged stress induced by the Single Prolonged Stress (SPS) protocol.

Material and methods

Animals and ethics statement

The study was conducted on 21 sexually mature male Wistar rats aged 8–10 weeks and weighing 210–230 g at the beginning of the experiment. Animals were housed under standard vivarium conditions: ambient temperature $22\pm 2^{\circ}\text{C}$, relative humidity 30–60%, and a 12:12 h light/dark cycle (lights on at 7:00 AM). Rats had free access to standard laboratory chow and drinking water ad libitum.

All experimental procedures were carried out in accordance with the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, 1986). The study protocol was reviewed and approved by the Bioethics and Ethics Committee of Poltava State Medical University (Protocol No. 213, dated February 22, 2023).

Experimental design

Rats were randomly assigned to three experimental groups. Animals in Group 1 (control) received polyvinylpyrrolidone (PVP) at a dose of 180 mg/kg body

weight orally in aqueous solution, used as a flavonoid solubilizer [20]. In the other groups, following induction of PTSD-like conditions via the Single Prolonged Stress (SPS) protocol and subsequent laparotomy, animals were treated daily for 7 days via intragastric administration (using a feeding tube) with either PVP alone at 180 mg/kg (Group 2) or a quercetin-PVP complex ("Corvitin", PJSC SIC "Borshchahivskiy Chemical-Pharmaceutical Plant", Ukraine) at 200 mg/kg, corresponding to 20 mg/kg quercetin (Group 3).

Seven days after SPS, all rats underwent behavioral screening using the open field test to assess anxiety-like responses. Only animals displaying characteristic PTSD-like behavioral patterns such as reduced time spent in the centre of the arena (less than 20% of total test time), increased thigmotaxis, decreased locomotor activity, and prolonged freezing episodes [21, 22] were included in Groups 2 and 3, ensuring behavioral homogeneity of stress-exposed animals.

Following the 7-day treatment course with either PVP or quercetin-PVP complex, euthanasia was performed under thiopental sodium anesthesia in accordance with ethical standards. Blood samples were collected immediately via cardiac puncture into sterile tubes without anticoagulant, allowed to clot at room temperature for 30 minutes, and centrifuged at $3000 \times g$ for 15 minutes. Serum was carefully separated and stored for subsequent biochemical analyses.

Single prolonged stress model

SPS was induced by immobilizing rats in a dorsal position on a metal platform using surgical tape for 2 hours. This was followed by a forced swim test in a plexiglass cylinder filled with water at 24°C. The final step of the protocol involved inhalation exposure to sevoflurane vapor ("Sevoran", AbbVie S.r.l., Italy) until loss of consciousness. After the procedure, animals were housed in pairs in standard cages without further interventions for 7 days.

Surgical trauma model

Surgical trauma was simulated by laparotomy under intraperitoneal thiopental sodium anesthesia (AT "Kyivmedpreparat", Kyiv, Ukraine) at a dose of 50 mg/kg body weight. After antiseptic preparation of the abdominal skin, a midline incision approximately 1 cm long was made, followed by blunt dissection of the muscular and peritoneal layers. A loop of the small intestine was briefly exteriorized and gently palpated

for 10 seconds before being returned to the abdominal cavity. The surgical wound was closed in layers using polyglycolide suture material and an atraumatic needle (NPO "Biopolymer", Poltava, Ukraine), according to a previously described method [8].

Biochemical and immunoassay analyses

Serum cortisol concentration, used as a marker of acute stress response, was measured by spectrophotometry using a ULAB 101 spectrophotometer (China). The method is based on cortisol's reaction with nitroblue tetrazolium (IUPAC: 2,2'-bis(4-nitrophenyl)-5,5'-diphenyl-3,3'-(3,3'-dimethoxy-4,4'-diphenylene) ditetrazolium chloride; Sigma-Aldrich, USA) in methanolic medium with tetramethylammonium hydroxide pentahydrate, forming a red-orange chromogen with maximum absorbance at 510 nm [23].

Serum levels of tumor necrosis factor- α (TNF- α) and interleukins (IL-6 and IL-10) were determined by enzyme-linked immunosorbent assay (ELISA) using rat-specific, high-sensitivity kits: Rat TNF- α ELISA Kit (RAB0479-1KT), Rat IL-6 ELISA Kit (RAB0311-1KT), and Rat IL-10 ELISA Kit (RAB0246-1KT) (Sigma-Aldrich, USA). Optical density was measured at 450 nm using the Stat Fax 2100 microplate reader (Awareness Technology, Inc., USA) per the manufacturer's instructions.

Serum ceruloplasmin concentration, an acute-phase inflammatory marker, was assessed colorimetrically based on its ability to oxidize p-phenylenediamine, according to a previously described method [24].

Serum glucose levels were measured by the glucose oxidase method, based on the formation of a red-violet quinonimine chromogen, detected at 540 nm using the ULAB 101 spectrophotometer and a commercial reagent kit (HP009.02, LLC "Filisit-Diagnostika", Dnipro, Ukraine).

Fasting insulin levels were measured via ELISA using the Rat Ins1/Insulin ELISA Kit (RAB0904-1KT, Sigma-Aldrich, USA), following a 12-hour overnight fast. Optical density was read at 450 nm using the Stat Fax 2100 microplate reader. The homeostasis model assessment of insulin resistance (HOMA-IR) index was calculated as follows: $\text{HOMA-IR} = (\text{Fasting glucose [mmol/L]} \times \text{Fasting insulin [\mu U/mL]}) / 22.5$ [25].

Lipid profile was assessed by determining serum concentrations of total cholesterol (TC0102), high-density lipoprotein cholesterol (HDL; HDL0102), and triglycerides (TG0102) using enzymatic colorimetric methods and standardized reagent kits (Mindray

Bio-Medical Electronics Co., China). Optical density was measured on the ULAB 101 spectrophotometer within the wavelength range of 490–600 nm. Low-density (LDL) and very-low-density lipoprotein (VLDL) cholesterol concentrations were calculated using the Friedewald formula.

Statistical analysis

Statistical analysis of the obtained data was performed using Microsoft Excel with the Real Statistics 2019 add-in. The Shapiro–Wilk test was used to assess the normality of data distribution. Descriptive statistics, including the arithmetic mean (M) and standard error of the mean (m), were calculated, and results are presented as $M \pm m$. Since all datasets followed a normal distribution, one-way ANOVA was employed for group comparisons, followed by pairwise analysis using Student's t-test for independent samples and Tukey's Honestly Significant Difference (HSD) test. To control for type I error in multiple comparisons, the Dunn–Šidák correction was applied. Differences were considered statistically significant at $P < 0.05$.

Results

Effect of water-soluble quercetin on serum markers of acute stress and systemic inflammation following SPS and experimental surgical trauma

The combined exposure to SPS and subsequent laparotomy resulted in marked activation of neuroendocrine and inflammatory mechanisms, as evidenced by significant alterations in serum markers of stress and

immune response, consistent with our previous publication [16]. In Group 2 animals, serum cortisol concentration increased 2.4-fold ($P < 0.001$) compared to the control group, indicating pronounced hyperactivation of the hypothalamic-pituitary-adrenal axis (Table 1). Administration of the water-soluble form of quercetin led to a 43.9% reduction in cortisol levels ($P < 0.001$) relative to Group 2; however, this value remained significantly elevated compared to the control.

Serum TNF- α concentration in rats exposed to combined SPS and laparotomy increased by 1.8-fold, while IL-6 levels rose 5.5-fold compared to the control group (both $P < 0.001$), confirming the development of a pronounced systemic inflammatory response (SIR). Administration of the water-soluble form of quercetin led to a significant reduction in TNF- α by 42.1% and IL-6 by 85.2% (both $P < 0.001$) relative to Group 2, indicating a strong ability of the compound to suppress excessive proinflammatory cytokine production under combined psychoemotional and surgical stress.

IL-10 levels, representing an anti-inflammatory response, increased by 48.8% ($P < 0.01$) in the SPS + laparotomy group compared to control, likely as a compensatory mechanism in response to enhanced proinflammatory activity. Quercetin treatment resulted in a 41.0% ($P < 0.001$) decrease in IL-10 levels relative to Group 2, thereby restoring the IL-10/IL-6 ratio, which reflects reestablishment of cytokine balance. With quercetin, this ratio returned to near-control values and exceeded Group 2 levels by 319% ($P < 0.01$), demonstrating a pronounced anti-inflammatory effect.

Ceruloplasmin, an acute-phase protein and oxidative stress marker, increased 1.7-fold ($P < 0.001$) following combined SPS and surgical trauma. Quercetin administration reduced its concentration by 15.8%

Table 1: Effect of the water-soluble form of quercetin on acute stress and systemic inflammatory response markers in serum under experimental surgical trauma following single prolonged stress ($M \pm m$).

Parameters	Control rats (only PVP), n=7	SPS + subsequent laparotomy	
		+ PVP, n=7	+ Quercetin + PVP, n=7
Cortisol (nmol/L)	15.39 $\pm$ 0.67	36.71 $\pm$ 0.60 *	20.58 $\pm$ 0.43 *, **
TNF- α (pg/mL)	235.8 $\pm$ 7.9	430.6 $\pm$ 26.1 *	249.5 $\pm$ 19.3 **
IL-6 (pg/mL)	79.3 $\pm$ 10.3	448.1 $\pm$ 62.3 *	66.3 $\pm$ 10.6 **
IL-10 (pg/mL)	203.8 $\pm$ 18	303.3 $\pm$ 22.4 *	179.0 $\pm$ 10.6 **
IL-10/IL-6 ratio	2.9 $\pm$ 0.5	0.8 $\pm$ 0.1 *	3.27 $\pm$ 0.67 **
Ceruloplasmin (mg/L)	308.4 $\pm$ 6.5	527.6 $\pm$ 3.1*	444.5 $\pm$ 14.6 *, **

Note: * – $P < 0.05$ compared to findings in the control group; ** – $P < 0.05$ compared to findings in the rats of Group 2. IL – Interleukin; PVP – Polyvinylpyrrolidone; SPS – Single Prolonged Stress; TNF- α – Tumor Necrosis Factor-alpha.

Table 2: Effect of the water-soluble form of quercetin on carbohydrate metabolism markers in serum under experimental surgical trauma following single prolonged stress (M±m).

Parameters	Control rats (only PVP), n=7	SPS + subsequent laparotomy	
		+ PVP, n=7	+ Quercetin + PVP, n=7
Glucose (mmol/L)	4.83±0.26	6.47±0.06 *	4.59±0.20 **
Insulin (μU/mL)	37.1±2.7	159.2±33.1 *	103.0±20.5 *
HOMA-IR	8.0±0.8	45.5±9.3 *	22.6±3.1 *, **

Note: * – P<0.05 compared to findings in the control group; ** – P<0.05 compared to findings in the rats of Group 2. HOMA-IR – Homeostatic Model Assessment of Insulin Resistance; PVP – Polyvinylpyrrolidone; SPS – Single Prolonged Stress.

(P<0.001) compared to Group 2, indicating attenuation of the acute-phase response and partial normalization of redox status.

Effect of water-soluble quercetin on serum markers of carbohydrate metabolism following SPS and experimental surgical trauma

Rats exposed to SPS followed by surgical trauma showed significant disturbances in carbohydrate metabolism [16]. In Group 2, serum glucose concentration was 34% higher than in the control group (P<0.001), indicating the development of stress-induced hyperglycemia (Table 2). Quercetin administration led to a significant 29.1% decrease in glucose levels (P<0.001) compared to Group 2, suggesting partial restoration of glycemic control.

Similar trends were observed in insulin levels, which increased 4.3-fold (P<0.01) following SPS and surgical trauma compared to the control group. This hyperinsulinemia likely reflects compensatory activation of pancreatic β-cells in response to peripheral insulin resistance. However, administration of the

water-soluble form of quercetin did not result in statistically significant changes in insulin concentration compared to Group 2, indicating a lack of direct effect on hormone secretion under these conditions.

The HOMA-IR index in rats subjected to SPS and laparotomy increased by nearly 5.7-fold (P<0.01) relative to control, confirming the development of pronounced insulin resistance. Quercetin administration reduced this index by 50.3% compared to Group 2, indicating a significant improvement in tissue insulin sensitivity and overall carbohydrate metabolism.

Effect of the water-soluble form of quercetin on serum lipid profile under experimental surgical trauma and SPS

Rats exposed to SPS followed by surgical trauma exhibited significant disturbances in lipid metabolism, reflecting the development of a stress-induced dyslipidemic profile. These alterations included hypertriglyceridemia, accumulation of VLDL cholesterol, and a marked decrease in the anti-atherogenic HDL cholesterol fraction (Table 3).

Table 3: Effect of the water-soluble form of quercetin on serum lipid profile under experimental surgical trauma following single prolonged stress (M±m).

Parameters	Control rats (only PVP), n=7	SPS + subsequent laparotomy	
		+ PVP, n=7	+ Quercetin + PVP, n=7
Total cholesterol (mmol/L)	2.39±0.22	2.73±0.09	2.53±0.14
HDL cholesterol (mmol/L)	0.90±0.06	0.32±0.03 *	0.68±0.04 *, **
LDL cholesterol (mmol/L)	1.22±0.24	1.55±0.09	1.54±0.16
VLDL cholesterol (mmol/L)	0.27±0.02	0.86±0.04 *	0.31±0.02 **
TGs (mmol/L)	0.60±0.05	1.90±0.08 *	0.68±0.05 **

Note: * – P<0.05 compared to findings in the control group; ** – P<0.05 compared to findings in the rats of Group 2. HDL – High-Density Lipoprotein; LDL – Low-Density Lipoprotein; PVP – Polyvinylpyrrolidone; SPS – Single Prolonged Stress; TGs – Triglycerides; VLDL – Very-Low-Density Lipoprotein.

In the SPS + laparotomy group, total serum cholesterol levels did not differ significantly from the control group. However, HDL cholesterol levels were significantly reduced by 2.8-fold ($P < 0.001$), indicating a substantial suppression of the antiatherogenic component of the lipid profile. At the same time, both VLDL cholesterol and triglyceride concentrations increased by 3.2-fold ($P < 0.001$). LDL cholesterol levels in Group 2 animals did not show statistically significant changes compared to control values.

Administration of the water-soluble form of quercetin significantly improved disrupted lipid metabolism parameters. Specifically, treatment resulted in a 2.1-fold increase in HDL cholesterol levels compared to Group 2 ($P < 0.001$), indicating partial restoration of the anti-atherogenic component of the lipid profile. At the same time, VLDL cholesterol and triglyceride levels decreased by 64.0% and 64.2%, respectively, compared to Group 2 values (both $P < 0.001$). Total cholesterol and LDL cholesterol concentrations in quercetin-treated animals did not differ significantly from those observed in Group 2.

Discussion

The present study demonstrates that exposure to prolonged psychogenic stress modelled by the SPS paradigm, followed by surgical trauma, induces a pronounced systemic inflammatory response accompanied by significant disturbances in carbohydrate and lipid metabolism. Importantly, administration of the water-soluble form of quercetin effectively attenuated neuroendocrine hyperactivation, suppressed excessive proinflammatory signaling, and partially normalized metabolic homeostasis, underscoring its potential as a pathogenetically oriented modulator of stress-induced systemic dysfunction.

A key finding of this study is the marked elevation of serum cortisol following SPS combined with laparotomy, reflecting sustained hyperactivation of the hypothalamic–pituitary–adrenal (HPA) axis. Dysregulation of the HPA axis is a well-documented hallmark of PTSD and PTSD-like states and is closely linked to altered immune regulation and metabolic imbalance [26]. Chronic glucocorticoid exposure, particularly in the context of impaired glucocorticoid receptor sensitivity, promotes a paradoxical proinflammatory milieu, characterized by increased TNF- α , and IL-6 production [27, 28]. The significant elevations of these cytokines observed in the SPS + laparotomy group confirm the induction of a

robust SIR, consistent with previous experimental and clinical observations [29].

The moderate compensatory increase in IL-10 detected in stressed animals likely reflects an endogenous attempt to counterbalance excessive inflammation. However, the markedly reduced IL-10/IL-6 ratio indicates a pronounced shift toward a proinflammatory cytokine profile. Similar cytokine imbalances have been reported in both PTSD patients and animal models, where persistent low-grade inflammation contributes to long-term somatic comorbidities, including cardiovascular and metabolic diseases [30, 31].

Administration of the water-soluble form of quercetin significantly reduced circulating cortisol levels and markedly suppressed TNF- α and IL-6 production while restoring the IL-10/IL-6 ratio toward control values. These findings are consistent with extensive evidence demonstrating that quercetin exerts potent anti-inflammatory effects via NF- κ B inhibition and modulation of mitogen-activated protein kinase (MAPK) pathways [32]. Additionally, quercetin is known to activate Nrf2, thus enhancing endogenous antioxidant defenses and indirectly limiting redox-sensitive inflammatory cascades [19].

The observed reduction in serum ceruloplasmin further supports the ability of quercetin to attenuate the acute-phase response and oxidative stress. Ceruloplasmin is increasingly recognized not only as an acute-phase protein but also as an indicator of systemic redox imbalance under chronic stress conditions [33]. The partial normalization of ceruloplasmin levels in quercetin-treated animals suggests improved redox homeostasis and reduced inflammatory burden.

In the present study, combined SPS and surgical trauma induced pronounced hyperglycemia, hyperinsulinemia, and a marked increase in the HOMA-IR index, indicating the development of stress-associated insulin resistance. These findings align with growing evidence linking PTSD and chronic stress exposure to impaired glucose metabolism and increased risk of type 2 diabetes mellitus [34]. Mechanistically, chronic activation of the HPA axis and proinflammatory cytokines such as TNF- α and IL-6 interfere with insulin signaling pathways by promoting serine phosphorylation of insulin receptor substrate proteins and impairing glucose uptake in peripheral tissues [35].

Quercetin administration significantly reduced blood glucose levels and lowered the HOMA-IR index, indicating improved insulin sensitivity. Although insulin concentrations remained elevated, the reduction in insulin resistance suggests enhanced peripheral

responsiveness to insulin rather than direct suppression of pancreatic β -cell activity. Similar metabolic benefits of quercetin have been reported in experimental models of metabolic syndrome and chronic inflammation, where quercetin improved insulin signaling through activation of AMP-activated protein kinase (AMPK) and attenuation of inflammatory signaling [36, 37].

The dyslipidemic profile observed in stressed animals and characterized by elevated triglycerides and VLDL cholesterol alongside depletion of HDL cholesterol is consistent with stress-induced alterations in hepatic lipid metabolism and lipoprotein remodeling [38]. Proinflammatory cytokines and glucocorticoids promote hepatic VLDL synthesis while impairing reverse cholesterol transport, thereby reducing HDL cholesterol levels [39, 40].

Quercetin treatment markedly improved the lipid profile, particularly by restoring HDL-CH levels and reducing VLDL-CH and triglycerides. These effects are in agreement with previous studies demonstrating that quercetin enhances cholesterol efflux via upregulation of ATP-binding cassette transporters (ABCA1) and suppresses hepatic lipogenesis through downregulation of sterol regulatory element-binding protein-1c (SREBP-1c) [41, 42]. The lack of significant changes in total and LDL cholesterol may reflect the relatively short duration of the intervention, suggesting that longer treatment periods may be required to affect these parameters.

Collectively, the results of this study support the concept that combined psychogenic and surgical stress acts synergistically to induce a systemic proinflammatory and pro-metabolic disturbance state that extends beyond isolated stress models. This condition closely resembles the complex somatic phenotype observed in PTSD patients with comorbid metabolic and cardiovascular disorders [43]. By targeting multiple upstream regulatory pathways, including redox-sensitive transcription factors and inflammatory mediators, quercetin demonstrates a broad-spectrum protective effect that may be particularly valuable in stress-associated systemic pathologies.

Conclusions

Quercetin, administered as a water-soluble quercetin-polyvinylpyrrolidone complex, significantly mitigated the systemic effects of combined prolonged stress and subsequent surgical trauma in rats. It partially reduced serum cortisol and ceruloplasmin levels,

markedly suppressed TNF- α and IL-6, and restored the IL-10/IL-6 ratio toward control values, indicating effective attenuation of the stress-induced systemic inflammatory response.

Quercetin improved glucose-insulin homeostasis primarily by lowering blood glucose and significantly reducing HOMA-IR, despite persistently elevated insulin levels relative to intact controls. Additionally, it substantially corrected lipid abnormalities by increasing HDL cholesterol and reducing triglycerides and VLDL cholesterol, without significantly affecting total or LDL cholesterol levels.

Collectively, these findings indicate that water-soluble quercetin provides significant protection against inflammation- and stress-related metabolic disturbances following surgical injury in a PTSD-like stress model, highlighting its potential as an adjunctive therapeutic approach to reduce systemic inflammatory response and cardiometabolic risk under conditions of combined psychoemotional and surgical stress.

Conflict of interest

The authors declare no conflict of interest.

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