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Water-soluble quercetin attenuates oxidative and nitrosative stress and connective tissue disruption in the small intestine of rats exposed to surgical trauma following acute prolonged stress

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This study aimed to evaluate the effects of a water-soluble quercetin formulation on markers of oxidative and nitrosative stress, nitric oxide synthase (NOS) system parameters, and extracellular matrix (ECM) degradation in the small intestine of rats subjected to surgical trauma following acute prolonged stress. Male Wistar rats (n = 21) were randomized into three groups: Group 1 (Control) - animals receiving polyvinylpyrrolidone (PVP) at a dose of 180 mg/kg body weight administered orally in aqueous solution, used as a flavonoid solubilizer; Group 2 - rats subjected to single prolonged stress (SPS) followed by laparotomy and treated with PVP alone at a dose of 180 mg/kg; Group 3 - rats exposed to SPS and subsequent laparotomy and treated with a quercetin-PVP complex (Corvitin) at a dose of 200 mg/kg, corresponding to 20 mg/kg of quercetin. After seven days of treatment, jejunal tissues were analyzed for superoxide production, NOS activity, peroxynitrite levels, and biochemical markers of ECM degradation. Combined psychological and surgical stress markedly increased superoxide generation from mitochondrial, microsomal, and NADPH oxidase sources, as well as total NOS activity and peroxynitrite formation, while suppressing constitutive NOS (cNOS) activity and the cNOS coupling index. ECM degradation was evidenced by elevated hydroxyproline, hexuronic acid, and N-acetylneuraminic acid levels. Treatment with water-soluble quercetin significantly reduced superoxide and peroxynitrite production (by 30-40%), suppressed inducible NOS (iNOS) activity (by 43%), and restored cNOS coupling. ECM degradation markers were simultaneously reduced by 13-15%, indicating preservation of collagen and glycoprotein integrity. Thus, water-soluble quercetin was associated with attenuation of oxidative and nitrosative stress, as well as a reduction in biochemical markers of intestinal connective tissue degradation under combined psychological and surgical trauma. These findings suggest that water-soluble quercetin acts as a pleiotropic modulator of redox homeostasis and may serve as an adjunct therapeutic agent for preventing intestinal injury associated with post-traumatic stress and surgical intervention.

Key words: quercetin; oxidative and nitrosative stress; small intestine; post-traumatic stress disorder; surgical trauma; nitric oxide synthase; extracellular matrix degradation.

INTRODUCTION

Post-traumatic stress disorder (PTSD) is one of the most common and debilitating consequences of extreme psychological trauma, particularly under conditions of prolonged military conflict. Since the onset of the full-scale invasion of Ukraine in 2022, the prevalence of PTSD has risen dramatically among both military personnel and civilians, reflecting widespread exposure to chronic stress and trauma [1]. Beyond its neuropsychiatric manifestations, PTSD is now recognized as a systemic pathological condition involving dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, chronic low-grade inflammation, oxidative stress, and metabolic disturbances [2]. These systemic alterations contribute to multi-organ injury, establishing a link between psychological stress and peripheral organ dysfunction.

Experimental and clinical studies have shown

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that activation of redox-sensitive signaling pathways under prolonged stress leads to overproduction of reactive oxygen and nitrogen species (ROS/RNS), mitochondrial impairment, and oxidative modification of biomolecules [3]. When psychological stress is compounded by physical injury, such as surgical trauma, these processes are further intensified, producing a synergistic systemic inflammatory response (SIR) phenotype characterized by cytokine hyperproduction, endothelial dysfunction, and extracellular matrix (ECM) degradation [4]. The small intestine, as a metabolically active and highly vascularized organ, is particularly susceptible to oxidative and nitrosative injury during such conditions, resulting in increased mucosal permeability, collagen fragmentation, and glycoprotein loss [5].

Our previous studies demonstrated that laparotomy following single prolonged stress (SPS) in rats induces a pronounced systemic inflammatory and metabolic response, characterized by hyperactivation of the hypothalamic–pituitary–adrenal axis, elevated levels of pro-inflammatory cytokines (tumor necrosis factor-α and interleukin-6), oxidative stress, and lipid peroxidation, all indicative of a systemic inflammatory response phenotype [6]. Experimental studies have shown that severe stress and systemic inflammatory conditions are associated with oxidative and nitrosative stress, activation of nuclear factor kappa B (NF-κB), and suppression of nuclear factor erythroid 2-related factor 2 (Nrf2)-dependent antioxidant responses in cardiovascular and gastrointestinal tissues [7]. These molecular alterations have been linked to extracellular matrix degradation, collagen fragmentation, impaired epithelial barrier integrity, and depletion of endogenous antioxidant defense systems [8]. Moreover, pharmacological modulation of redox-sensitive signaling pathways using flavonoids has been reported to attenuate oxidative injury and to limit extracellular matrix degradation in models of lipopolysaccharide-induced [9].

Polyphenolic compounds such as quercetin are potent natural modulators of redox-sensitive transcription factors, capable of scavenging free radicals, suppressing NF-κB activation, and enhancing Nrf2-mediated antioxidant responses [10, 11]. However, the clinical translation of quercetin has been limited by its low water solubility and poor bioavailability. Recent advances in pharmaceutical formulation have yielded water-soluble quercetin derivatives with significantly improved absorption and systemic distribution [12]. These formulations demonstrate enhanced antioxidant and anti-inflammatory activity in experimental models of SIR and oxidative stress.

Given the important role of oxidative and nitrosative stress in stress-associated intestinal injury, water-soluble quercetin may represent a potentially beneficial adjunctive approach to limiting intestinal connective tissue damage under conditions of combined psychological and surgical stress. Previous studies have demonstrated antioxidant and anti-inflammatory properties of quercetin; however, its effects in combined SPS-associated and surgical intestinal injury remain insufficiently characterized. In the present study, we hypothesized that quercetin administration would be associated with attenuation of oxidative damage and extracellular matrix degradation, possibly through modulation of redox-sensitive signaling pathways involved in inflammatory and antioxidant responses.

Therefore, this study aimed to evaluate the effects of a water-soluble quercetin formulation on oxidative and nitrosative stress markers, nitric oxide synthase system parameters, and extracellular matrix degradation in the small intestine of rats subjected to surgical trauma following acute prolonged stress.

METHODS

The study was carried out on 21 male Wistar rats weighing 210-230 g. Animals were housed under standard vivarium conditions (ambient temperature: 22 ± 2°C; relative humidity:

30-60%) with a 12:12 h light/dark cycle, free access to standard laboratory chow, and water ad libitum. Experimental procedures complied with the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, 1986) and the provisions of EU Directive 2010/63/EU on the protection of animals used for scientific research. The ethical review and approval for this study were provided by the Bioethics and Ethics Committee of Poltava State Medical University (Protocol No. 213, February 22, 2023).

Rats were randomly assigned to three experimental groups: Group 1 (Control) - animals receiving polyvinylpyrrolidone (PVP) at a dose of 180 mg/kg body weight administered orally in aqueous solution, used as a flavonoid solubilizer [12]; Group 2 (SPS with laparotomy and PVP treatment) – rats subjected to SPS followed by laparotomy and treated with PVP alone at a dose of 180 mg/kg; Group 3 (SPS with laparotomy and quercetin–PVP complex treatment) – rats exposed to SPS and subsequent laparotomy and treated with a quercetin–PVP complex ("Corvitin", PJSC SIC "Borshchahivskiy Chemical-Pharmaceutical Plant", Ukraine) at a dose of 200 mg/kg, corresponding to 20 mg/kg of quercetin. Following SPS exposure, animals in Groups 2 and 3 underwent laparotomy and then received daily intragastric administration of the assigned treatment for 7 consecutive days.

SPS was induced by immobilizing rats for 2 h on a metal platform with surgical tape restraints. Following this, animals underwent a forced swim test in a water-filled Plexiglas cylinder maintained at 24°C. Lastly, the rats were exposed to sevoflurane vapor ("Sevoran", "AbbVie S.r.l.", Italy) until loss of consciousness. After the procedure, the animals were housed in pairs and remained undisturbed for seven days. This SPS paradigm is widely validated as an experimental model of post-traumatic stress disorder, eliciting behavioral and physiological changes akin to the human condition [13]. Laparotomy was performed under intraperitoneal thiopental anesthesia ("Kyivmedpreparat", Ukraine, 50 mg/kg). After antiseptic treatment of the abdominal skin, a 1 cm midline incision was made, followed by blunt dissection through the muscular and peritoneal layers. A segment of the small intestine was briefly exteriorized and gently palpated for 10 s before repositioning. The incision was closed in anatomical layers using polyglycolide suture material and an atraumatic needle ("Biopolymer", Ukraine) as previously described [4].

On the seventh day of the experiment, rats were anesthetized using thiopental sodium and euthanized in accordance with institutional ethical guidelines. A 10% homogenate of jejunal tissue was prepared by excising a standardized 5 cm segment of the jejunum, which was immediately rinsed in ice-cold 0.9% sodium chloride solution to remove luminal contents. The tissue was then homogenized in a chilled 0.1 M Tris-HCl buffer (pH 7.4) at a 1:10 weight-to-volume ratio (w/v) to ensure consistency across samples. Homogenization was performed under cold conditions to preserve enzymatic and oxidative parameters.

Superoxide anion radical ($\bullet O_2^-$) production in the jejunal homogenate was assessed using the nitroblue tetrazolium (NBT) reduction assay based on spectrophotometric detection of diformazan formation, as previously described [14]. Nitroblue tetrazolium (NBT; IUPAC name: 2,2′-bis(4-nitrophenyl)-5,5′-diphenyl-3,3′-(3,3′-dimethoxy-4,4′-diphenylene) ditetrazolium chloride; "Sigma-Aldrich", USA) was used as the chromogenic reagent. 0.1 g of intestinal tissue was homogenized in 0.9 ml phosphate buffer (pH 7.4). Homogenate aliquots were incubated under different experimental conditions to assess $\bullet O_2^-$ generation from specific cellular sources. β-Nicotinamide adenine dinucleotide phosphate reduced tetrasodium salt hydrate (NADPH, ≥97%; "Sigma-Aldrich", USA) was used as an inducer of $\bullet O_2^-$ production by the microsomal electron transport chain (ETC) and NO-synthases, whereas β-nicotinamide adenine dinucleotide reduced disodium salt hydrate

(NADH, ≥97%; "Sigma-Aldrich", USA) was used to evaluate mitochondrial ETC-derived superoxide production. $\bullet O_2^-$ generation by tissue phagocytes was assessed after stimulation with *Salmonella typhi* lipopolysaccharide ("Sigma-Aldrich", USA) in the presence of Triton X-100. Following incubation with 0.2% NBT solution in Tris buffer (pH 7.4), the resulting diformazan was extracted using a dimethyl sulfoxide-chloroform mixture (2:1), and absorbance was measured at 540 nm using a ULAB 101 spectrophotometer (China).

Total NOS activity was assessed by measuring NO_2^- generation after a 30-minute incubation of 10% intestinal homogenates in an incubation medium containing 2.5 ml of 0.1 M Tris-HCl buffer (pH 7.4), 0.3 ml of 320 mmol/l L-arginine ("Sigma-Aldrich", USA), and 0.1 ml of 1 mM NADPH [14]. Constitutive NOS (cNOS) activity was measured in parallel samples supplemented with aminoguanidine hydrochloride (1% w/v, 98%; "Sigma-Aldrich", USA), a selective inhibitor of inducible NOS isoforms (iNOS). The iNOS-specific activity was derived by subtracting cNOS activity from total NOS activity. Protein concentrations were determined via the Biuret method and used to normalize enzyme activities. To evaluate NOS coupling efficiency, a cNOS coupling index was calculated as the ratio of cNOS activity to NADPH-dependent superoxide production rate, reflecting the balance between NO and superoxide outputs from NOS isoforms.

Concentration of peroxynitrites of alkali and alkali-earth metals in the jejunal homogenate was determined spectrophotometrically based on the oxidation of potassium iodide (≥99.0%, "Sigma-Aldrich", USA), as previously described [14]. The method is based on the ability of peroxynitrite to oxidize iodide ions with the formation of triiodide anion, which exhibits a characteristic absorbance at 355 nm. 0.1 ml of 10% tissue homogenate was added to 3.9 ml phosphate buffer (pH 7.0), followed by the addition of 1 ml freshly prepared 5% potassium iodide solution. After 1 min incubation at room temperature, absorbance was measured at 355 nm against a reagent blank using a ULAB 101 spectrophotometer (China). Peroxynitrite concentration was calculated using the molar extinction coefficient of triiodide and expressed as μmol/g tissue.

The extent of connective tissue degradation was assessed by quantifying specific biochemical markers of extracellular matrix breakdown in jejunal homogenates. These included free hydroxyproline (a product of collagen degradation), hexuronic acids (indicative of glycosaminoglycan depolymerization), and N-acetylneuraminic acid (a marker of disrupted sialoglycoprotein integrity). All spectrophotometric measurements were performed using a ULAB 101 spectrophotometer (China).

Statistical processing was performed using Microsoft Excel with the Real Statistics 2019 plugin. The Shapiro–Wilk test was used to verify data normality. Results are presented as mean ± standard error of the mean (M ± m). One-way ANOVA was applied for comparisons among groups with normal distribution, followed by Student's t-test for pairwise analysis and Tukey's HSD post hoc test. The Dunn–Šidák correction was employed to reduce type I error risk during multiple comparisons. A $P < 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

The combined exposure to SPS and surgical trauma resulted in a marked elevation of $O_2^{\bullet-}$ production in the jejunal tissue of rats, indicating pronounced activation of oxidative pathways associated with different sources (Table 1). In the Group II, $\bullet O_2^-$ generation from microsomal ETC and NOS increased by 72.7% compared with control values. Similarly, mitochondrial ETC-derived superoxide production rose by 70.7% relative to controls, while phagocytic NADPH oxidase-dependent production increased nearly twofold (+99.2%). These findings confirm an extensive activation of both intracellular and membrane-associated oxidant-generating

Table 1. Effect of water-soluble quercetin on the superoxide anion radical production (nmol/s per g of tissue) in the jejunum of rats exposed to single prolonged stress and subsequent laparotomy (M ± m, n = 7)

Sources of superoxide anion radical generation	Control	Single prolonged stress followed by laparotomy and polyvinylpyrrolidone administration	Single prolonged stress followed by laparotomy with quercetin and polyvinylpyrrolidone administration
Microsomes and nitric oxide synthase	22.58±0.53	39.00±0.25 *	23.41±1.31 **
Mitochondria	24.29±0.51	41.46±0.31*	35.78±1.24 *,**
Phagocytic nicotinamide adenine dinucleotide phosphate oxidase	2.40±0.05	4.78±0.06 *	3.34±0.02 *,**

Note (here and in Tables 2; 3): *P < 0.05 compared to findings in the control group; **P < 0.05 compared to findings in the rats of Group 2.

systems following combined psychological and surgical stress.

Administration of water-soluble quercetin (Group III) significantly mitigated these alterations. $\bullet O_2^-$ generation from microsomal ETC and NOS decreased by 40.0% compared with untreated SPS with laparotomy rats, returning values close to those observed in the control group. Quercetin treatment also reduced mitochondrial ETC–derived superoxide production by 13.7% relative to Group II, while the phagocytic NADPH oxidase–mediated component was lowered by 30.1%.

These results demonstrate that water-soluble quercetin effectively limits excessive $\bullet O_2^-$ formation from multiple enzymatic sources, suggesting its ability to preserve mitochondrial and microsomal redox balance and to suppress phagocytic oxidative burst activity under conditions of combined stress and trauma.

Combined exposure to SPS and surgical trauma produced a pronounced activation of NOS pathways in the jejunal tissue of rats, indicating the development of nitrosative stress (Table 2). In the Group II, total NOS activity increased by 124% compared with control values (P < 0.001), reflecting a global upregulation of nitric oxide production. This rise was mainly attributed to the inducible NOS (iNOS) isoform, whose activity showed a 172% elevation relative to the control group. In contrast, constitutive NOS (cNOS) activity was markedly suppressed by 76.0% compared with control rats. As a result, the cNOS coupling index, reflecting the efficiency of electron transfer and coupling of NO synthesis, declined more than sevenfold (–86.5%) versus control levels, indicating a severe shift toward uncoupled, pro-oxidant NOS activity. Concomitantly, the concentration of peroxynitrites of alkali and alkali-earth metals, stable end products of the interaction between $\bullet O_2^-$ and nitric oxide, increased by 67.2% relative to controls, thus confirming excessive RNS formation under the combined stress condition.

Administration of water-soluble quercetin (Group III) effectively attenuated these disturbances. Total NOS activity decreased by 39.8% relative to the untreated SPS with laparotomy and PVP treatment rats, largely due to suppression of iNOS activity (–43.1%) and partial recovery of cNOS activity (+115%) compared with Group II. Importantly, the cNOS coupling index increased by 270% relative to the SPS with laparotomy and PVP treatment group, reflecting restoration of NOS functionality and

Table 2. Effect of water-soluble quercetin on the reactive nitrogen species formation in the jejunum of rats exposed to single prolonged stress and subsequent laparotomy (M ± m, n = 7)

Parameters	Control	Single prolonged stress followed by laparotomy and polyvinylpyrrolidone administration	Single prolonged stress followed by laparotomy with quercetin and polyvinylpyrrolidone administration
Nitric oxide synthase activity, μmol (NO_2^-) / min per g of protein			
total	8.56±0.61	19.20±0.49*	11.56±0.46*,**
constitutive	1.67±0.13	0.40±0.08*	0.86±0.10*,**
inducible	6.89±0.53	18.80±0.43*	10.70±0.41*,**
Constitutive nitric oxide synthase coupling index	0.074±0.005	0.010±0.002*	0.037±0.005*,**
Peroxynitrites of alkali and alkali-earth metals concentration, μmol/g of tissue	1.34±0.04	2.24±0.04*	1.83±0.04*,**

improved redox coupling. The tissue content of peroxynitrites was simultaneously reduced by 18.3% compared with Group II ($P < 0.05$), demonstrating attenuation of nitrosative stress and improved redox homeostasis in the intestinal wall.

Taken together, these findings indicate that water-soluble quercetin markedly limits nitrosative stress in the jejunum by normalizing the balance between iNOS and cNOS activities, restoring proper NOS coupling, and reducing peroxynitrite accumulation under conditions of combined psychological and surgical stress.

Combined exposure to SPS and surgical trauma induced pronounced degradation of connective tissue biopolymers in the jejunal wall, reflecting the activation of catabolic and oxidative processes within the ECM (Table 3). In the Group II, free hydroxyproline content, a marker of collagen breakdown, increased by 73.8% relative to control values, indicating enhanced proteolytic cleavage of fibrillar collagen. Similarly, hexuronic acid levels, which reflect degradation of glycosaminoglycans, were elevated by 74.0% compared with controls. The N-acetylneuraminic acid concentration, an index of sialoprotein and glycoprotein desialylation, also rose significantly - by 74.5% compared to control animals.

Treatment with water-soluble quercetin effectively counteracted these catabolic changes. The level of free hydroxyproline decreased by 14.5% relative to the untreated SPS with laparotomy and PVP treatment rats, reflecting partial preservation of collagen structure. Hexuronic acid content declined by 12.8% compared with Group II, suggesting attenuation of glycosaminoglycan depolymerization. Likewise, N-acetylneuraminic acid levels were reduced by 13.5% vs Group II, indicating stabilization of glycoprotein components of the intestinal mucosa.

These results demonstrate that water-soluble quercetin markedly limits the depolymerization of key ECM macromolecules under conditions of systemic inflammatory and oxidative stress.

The increase in $\bullet O_2^-$ generation from both mitochondrial and microsomal electron transport chains, as well as from phagocytic NADPH oxidase, confirms that combined psychological and surgical stress triggers a multilevel oxidative response. These findings are consistent with

Table 3. Effect of water-soluble quercetin on the depolymerization of connective tissue biopolymers in the jejunum of rats exposed to single prolonged stress and subsequent laparotomy (M ± m, n = 7)

Parameters	Control	Single prolonged stress followed by laparotomy and polyvinylpyrrolidone administration	Single prolonged stress followed by laparotomy with quercetin and polyvinylpyrrolidone administration
Free hydroxyproline, μmol/g of tissue	3.85±0.07	6.69±0.07 *	5.72±0.20 *,**
Hexuronic acid, μmol/g of tissue	2.15±0.05	3.74±0.02 *	3.26±0.11 *,**
N-acetylneuraminic acid content, μmol/g of tissue	5.02±0.08	8.76±0.10 *	7.58±0.18 *,**

previous observations in cardiac tissue, where SPS combined with laparotomy enhanced ROS production [7]. Similar to our earlier results, the current data indicate that mitochondrial ETC dysfunction is a major contributor to oxidative stress, amplifying $\bullet O_2^-$ leakage and impairing ATP generation.

The pronounced increase in total NOS activity, driven predominantly by iNOS up-regulation, and the simultaneous cNOS activity suppression, confirm a shift toward a pro-inflammatory and nitrosative state. The sevenfold reduction in the cNOS coupling index indicates partial uncoupling of NOS isoforms, leading to $\bullet O_2^-$ rather than NO production, a hallmark of nitrosative stress. This phenomenon is consistent with reports indicating that chronic stress and PTSD promote NF-κB-dependent iNOS expression while concurrently suppressing eNOS-mediated vasoprotective signaling [15]. The concurrent increase in peroxynitrite concentrations further supports the presence of RNS overproduction and NO/ROS imbalance, which contribute to tissue injury through tyrosine nitration, lipid oxidation, and collagen fragmentation [16].

Treatment with water-soluble quercetin significantly reduced both oxidative and nitrosative stress markers, suggesting that its protective effects are mediated by modulation of redox-sensitive signaling pathways. The observed reduction in $\bullet O_2^-$ generation from multiple cellular compartments is consistent with the flavonoid's ability to scavenge free radicals and to modulate mitochondrial redox metabolism [17].

The 40% decrease in total NOS activity and restoration of the cNOS/iNOS balance indicate that quercetin not only inhibits iNOS overactivation but also improves coupling efficiency of the constitutive NOS isoforms. Similar effects have been reported, demonstrating that quercetin suppresses iNOS expression by inhibiting NF-κB nuclear translocation, while concurrently activating Nrf2-mediated transcription of antioxidant enzymes such as heme oxygenase-1 and superoxide dismutase [18].

The accumulation of free hydroxyproline, hexuronic acid, and N-acetylneuraminic acid in the SPS with laparotomy rats demonstrates an extensive depolymerization of ECM components such as collagen fibers, glycosaminoglycans, and glycoproteins within the intestinal wall. This pattern indicates enhanced proteolytic activity of matrix metalloproteinases (MMPs) and glycosidases, likely triggered by oxidative modification of structural proteins and activation of NF-κB-dependent inflammatory cascades. Comparable ECM degradation has been observed in other SIR models and stress-induced intestinal injury [19].

Water-soluble quercetin effectively limited these catabolic processes, reducing hydroxyproline, hexuronic acid, and N-acetylneuraminic acid levels by approximately 13-15% compared with untreated animals. These results may indicate partial preservation of extracellular matrix organization and attenuation of processes associated with matrix degradation. Previous investigations have shown that quercetin downregulates MMP-2 and MMP-9 expression in tissues via inhibition of NF-κB signaling [20]. Moreover, the enhanced water solubility and bioavailability of the PVP–quercetin complex used in this study likely improved tissue distribution, amplifying its local antioxidant and anti-inflammatory effects [12].

The present study extends previous observations by providing additional evidence that water-soluble quercetin may contribute to attenuation of intestinal oxidative damage and extracellular matrix degradation under combined psychological and surgical stress conditions, potentially relevant to post-traumatic and postoperative complications.

Limitations. Several limitations of the present study should be acknowledged. First, although the observed attenuation of oxidative–nitrosative stress and partial preservation of extracellular matrix integrity after quercetin administration are consistent with modulation of redox-sensitive signaling pathways, the activity of key transcriptional regulators, including NF-κB and Nrf2, was not directly evaluated. Consequently, the proposed involvement of NF-κB suppression and Nrf2 activation should be interpreted as inferential and based on well-established evidence from previous studies, rather than as direct mechanistic confirmation within the current experimental design. Second, the study employed a single dose and fixed treatment duration of water-soluble quercetin. Therefore, dose–response relationships, time-dependent effects, and the optimal therapeutic window could not be determined. Future studies incorporating multiple dosing regimens and treatment durations are warranted to better define the pharmacodynamic profile of quercetin under combined psychological and surgical stress conditions.

Future investigations should include direct molecular analyses of NF-κB/Nrf2 signaling (e.g., Western blotting, immunohistochemistry, or gene expression profiling), expanded experimental group designs, and comprehensive dose–response assessments to clarify the causal mechanisms underlying the protective effects of quercetin and to further substantiate its therapeutic potential in stress-associated intestinal injury.

CONCLUSIONS

1. Combined exposure to acute prolonged stress and surgical trauma causes marked oxidative and nitrosative stress in the small intestine. This condition is characterized by enhanced activation of pro-oxidant enzymatic systems, excessive generation of reactive oxygen and nitrogen species, and pronounced degradation of extracellular matrix components. These changes are reflected by increased superoxide and peroxynitrite production, predominant activation of inducible nitric oxide synthase with concomitant uncoupling of constitutive isoforms, and elevated levels of biochemical markers of connective tissue depolymerization.

2. Treatment with water-soluble quercetin significantly attenuated these pathological alterations. Quercetin reduced oxidative and nitrosative stress, suppressed inducible nitric oxide synthase activity, improved constitutive nitric oxide synthase coupling, and partially restored nitric oxide synthase homeostasis. In addition, quercetin limited extracellular matrix degradation, thereby preserving the structural integrity of collagenous and glycoprotein components of the intestinal wall.

The authors of this study confirm that the research and publication of the results were not associated with any conflicts regarding commercial or financial relations, relations with organizations and/or individuals who may have been related to the study, and interrelations of co-authors of the article.

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ВОДОРОЗЧИННИЙ КВЕРЦЕТИН ПОСЛАБЛЮЄ ОКСИДАТИВНИЙ І НІТРОЗАТИВНИЙ СТРЕС ТА ПОРУШЕННЯ СПОЛУЧНОЇ ТКАНИНИ ТОНКОЇ КИШКИ У ЩУРІВ ЗА УМОВ ХІРУРГІЧНОЇ ТРАВМИ ПІСЛЯ ГОСТРОГО ТРИВАЛОГО СТРЕСУ

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Досліджено вплив водорозчинного препарату кверцетин на показники оксидативного та нітрозативного стресу, параметри системи синтази оксиду азоту, а також на деградацію позаклітинного матриксу в тонкій кишці щурів, які зазнали хірургічної травми після гострого тривалого стресу. Експеримент проведено на самцях щурів лінії Вістар (n = 21), яких було рандомізовано на 3 групи: 1-ша (контрольна) – тварини, які отримували полівінілпіролідон (ПВП) у дозі 180 мг/кг перорально у водному розчині як солюбілізатор флавоноїду; 2-га – щури, яким моделювали одноразовий тривалий стрес (ОТС) з подальшою лапаротомією та введенням ПВП (180 мг/кг); 3-тя – тварини після ОТС і лапаротомії, яким вводили комплекс кверцетину з ПВП (корвітин) у дозі 200 мг/кг (еквівалент 20 мг/кг кверцетину). Через 7 діб досліджували тканини порожньої кишки з визначенням продукції супероксидного аніон-радикала ($\bullet O_2^-$), активності NO-синтази (NOS), вмісту пероксинітриту та біохімічних маркерів деградації позаклітинного матриксу. Комбінований вплив психоемоційного та хірургічного стресу супроводжувався значним підвищенням генерації $\bullet O_2^-$, мітохондріального, мікросомального та НАДФН-оксидазного походження, зростанням загальної активності NOS і концентрації пероксинітриту, а також зниженням активності конститутивних ізоформ NOS (cNOS) і індексу її спряження. Ознаки деградації позаклітинного матриксу підтверджувалися підвищенням вмісту оксипроліну, гексуронових кислот і N-ацетилнейрамінової кислоти. Застосування водорозчинного кверцетину достовірно знижувало продукцію $\bullet O_2^-$ і пероксинітриту (на 30–40%) пригнічувало активність індуцибельної NOS (на 43%) та відновлювало індекс спряження cNOS. Водночас відзначалося зниження маркерів деградації позаклітинного матриксу на 13–15%, що свідчить про збереження структури колагену та глікопротеїнів. Таким чином, водорозчинна форма кверцетину зменшує вираженість оксидативного та нітрозативного стресу, а також знижує біохімічні прояви деградації сполучної тканини кишечника за умов поєднаної психологічної та хірургічної травми. Отримані результати свідчать про плейотропну дію кверцетину як модулятора редокс-гомеостазу та обґрунтовують доцільність його використання як допоміжного терапевтичного засобу для профілактики уражень кишечника при посттравматичному стресі та хірургічних втручаннях.

Ключові слова: кверцетин; оксидативний і нітрозативний стрес; тонка кишка; посттравматичний стресовий розлад; хірургічна травма; NO-синтаза; деградація позаклітинного матриксу.

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