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The ameliorating effect of Rutin on hepatotoxicity and inflammation induced by the daily administration of vortioxetine in rats

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Abstract

Background Vortioxetine (VORTX) is a potent and selective type of selective serotonin reuptake inhibitor (SSRI) that is mainly prescribed for treating major depression along with mood disorders as the first drug of choice. Limited previous findings have indicated evidence of liver injury and hepatotoxicity associated with daily VORTX treatment. Rutin (RUT), which is known for its antioxidant properties, has demonstrated several beneficial health actions, including hepatoprotection. Therefore the current study aimed to evaluate and assess the ameliorative effect of RUT against the hepatotoxic actions of daily low and high-dose VORTX administration.

Methods The experimental design included six groups of rats, each divided equally. Control, rats exposed to RUT (25 mg/kg), rats exposed to VORTX (28 mg/kg), rats exposed to VORTX (28 mg/kg) + RUT (25 mg/kg), rats exposed to VORTX (80 mg/kg), and rats exposed to VORTX (80 mg/kg) + RUT (25 mg/kg). After 30 days from the daily exposure period, assessments were conducted for serum liver enzyme activities, hepatotoxicity biomarkers, liver antioxidant endogenous enzymes, DNA fragmentation, and histopathological studies of liver tissue.

Results Interestingly, the risk of liver damage and hepatotoxicity related to VORTX was attenuated by the daily co-administration of RUT. Significant improvements were observed among all detected liver functions, oxidative stress, and inflammatory biomarkers including aspartate aminotransferase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH), albumin, malondialdehyde (MDA), superoxide dismutase (SOD), glutathione (GSH), glutathione S-transferase (GST), total protein, acid phosphatase, N-Acetyl-/β-glucosaminidase (β-*NAG*), β-Galactosidase (β-Gal), alpha-fetoprotein (AFP), caspase 3, and cytochrom-C along with histopathological studies, compared to the control and sole RUT group.

Conclusion Thus, RUT can be considered a potential and effective complementary therapy in preventing hepatotoxicity and liver injury induced by the daily or prolonged administration of VORTX.

Keywords SSRIs, Hepatotoxicity, Liver injury, DNA fragmentation, Apoptosis, Oxidative stress

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Background

Depression is a highly persistent, recurrent, and chronic disorder type. It is highly ranked as one of the leading causes of worldwide disability, affecting millions of people [1]. Depression symptoms are diverse and encompass a range of experiences such as low mood, loss of appetite, lack of interest migraine, cognitive impairment, and reduced energy. These directly impact the daily social life of individuals with depression and contribute significantly to the overall disease burden [1]. Additionally, depression results in direct alteration of the maintained balance between antioxidants and relative reactive oxygen species (ROS) by increasing oxidative stress levels. Antidepressant drugs are considered the most widely used drugs among the population. However, prolonged and excessive use of these drugs can lead to various risk factors and drawbacks, including liver injury, malnutrition-related chronic liver injury, inflammatory conditions, and HIV infection [2–6]. The selective serotonin reuptake inhibitor drug type (SSRI) is one of the most widely used antidepressant drugs which was first introduced in the early 80s for the alleviation of major depressive disorders, are associated with common and repetitive adverse effects, including hepatotoxicity and sexual dysfunction [7–9].

Drug-induced chronic liver injury is considered the fourth leading cause of liver damage among the population, and increasingly becoming a relevant matter of concern for physicians. Despite previously published data on antidepressant-induced liver injuries being relatively scarce, several patients treated with antidepressant drugs may develop hepatotoxicity and hepatitis on prolonged misuse [3, 10]. Liver damage is mainly unpredictable and idiosyncratic, and can also be influenced by factors such as drug dosage and duration of use. Depressed patients who are on SSRIs are more predisposed to liver injuries [9, 11]. Vortioxetine (VORTX) is a type of multimodal drug that modulates 5-hydroxytryptamine (5-HT) receptors and acts as an SSRI [11, 12]. It is highly indicated for the treatment of major depressive disorders. On the other hand, VORTX indirectly modulates glutamate and Gamma-aminobutyric acid (GABA) receptors by reducing both transmission [12]. Previous studies have indicated that SSRIs can lead to liver injuries, hepatitis, hepatotoxicity, and inflammation when used inappropriately or for extended periods [3, 9, 13, 14].

Flavonoids are a relatively large group type of polyphenolic compounds that play a crucial role in detoxifying free radicals and are highly abundant in vegetables, fruits, and medicinal plants. Rutin (RUT) is a famous type of glycosidic flavonoid and is more highly absorbed by humans than aglycones and can be found in tomato leaves, apples, onions, and tea [15–19]. The hepatoprotective, anti-inflammatory, and antioxidant effects of rutin are mainly attributed to its metabolite, quercetin. Upon daily oral administration of rutin, glycoside hydrolysis occurs, releasing quercetin metabolite [20]. The various pharmacological actions of rutin have been repeatedly stated among previously published preclinical and clinical studies. Rutin has previously shown therapeutic efficacy in various disease models such as rheumatoid arthritis, inflammatory bowel disease, inflammation, and metabolic syndrome, all of were attributed to its immunological and anti-inflammatory properties regulating pathways including nuclear factor kappa B (NF-κB), phosphoinositide 3-kinase (PI3K/Akt), mitogen-activated protein kinases (MAPK), Heme oxygenase-1 (HO-1), and Nuclear factor erythroid 2-related factor 2 (Nrf2) [20]. The administration of rutin also revoked the hepatotoxicity effects of the paclitaxel chemotherapeutic drug. It was shown that paclitaxel exerts different inflammatory actions by exaggerating the release of numerous inflammatory cytokines such as interleukin-17 A, interferon (INF), and tumor necrosis factor-alpha (TNF-α) [21]. Meanwhile [21], stated that rutin daily administration protected the liver from damageable effects by ameliorating elevated liver enzymes, and oxidative stress along with knocking off NF-κB and TNF-α receptors. It was also reported that rutin exerts a protective effect against DNA damage due to its wide antioxidant potential actions. Additionally, rutin administration boosted the antioxidative stress, anti-apoptotic, and anti-inflammatory defense mechanisms against doxorubicin toxicity in rats by suppressing TNF-α and regulating the Nrf2 transcription factor [22]. The daily base rutin administration was reported to protect diabetic patients from different symptoms along with attenuating cytotoxicity and oxidative stress in human erythrocytes [23, 24]. also reported that rutin revoked the nephrotoxicity induced by valproic acid administration in rats by suppressing the release of the signal transducer and activator of transcription 3, BAX, Janus Kinase 2, and caspase-3 levels along with increasing BCL2 expression. Rutin was also reputed to ameliorate intestinal toxicity and peptic ulcer by exerting antihistaminic actions, increasing the production of prostaglandin, and exhibiting antioxidant capacity in addition to scavenging oxidative stress [25]. It was also previously demonstrated that rutin exerts synergistic effects along with the daily administration of vitamin C in decreasing MDA, triglycerides, TNF-α, and C-reactive protein (CRP) in addition to exerting a protective effect against DNA damage among severe hemodialysis patients [26]. Therefore, the present study aims to investigate the main hepatoprotective actions of RUT against the hepatotoxic effects of VORTX administration in rats at different pharmacological doses in addition to highlighting its role in hindering and alleviating the drawbacks of VORTX-induced liver injury.

Materials and methods

Materials

Vortioxetine hydrobromide (VORTX-catalogue name: SML3388) was purchased and obtained from Sigma Chemical, Germany. Rutin hydrate (RUT) was also purchased and obtained from Sigma Chemical, Germany. All other used chemicals were freshly prepared and of high analytical grade.

Animals and experimental design

The necessary required permission was obtained from the Ethical Committee of the National Organization of Drug Control and Research (NODCAR) approval number (NODCAR/II/8/2023) guided by the required 3Rs principles (Replacement, Reduction, and Refinement). The health and physical fitness condition of the experimental animals used in this study were highly monitored throughout the whole experimental design. Prior to the commencement of the study, all rats underwent a thorough health assessment by a licensed veterinarian to ensure they were free from any pre-existing undetected health conditions. Before the start of the experimental design, the thirty-six male healthy Albino rats of weight (150–170 gram), and age (9–10 weeks) were all weighed to calculate their initial weight and then were equally divided into six required groups as follows:

1. **Control Rats (G1)**: The included rats administrated saline solution orally for three weeks.
2. **Rats exposed to RUT (G2)**: The included rats administrated RUT at a dose of 25 mg/kg/daily/orally for three weeks with certain modifications [27].
3. **Rats exposed to VORTX low dose (G3)**: The included rats administrated VORTX at a dose of 28 mg/kg/daily/orally for three weeks with certain modifications [28].
4. **Rats exposed to VORTX low dose + RUT (G4)**: The included rats concurrently administrated VORTX at a dose of 28 mg/kg/daily/orally [28] and RUT at a dose of 25 mg/kg/daily/orally [27] for three weeks with certain modifications.
5. **Rats exposed to VORTX high dose (G5)**: The included rats administrated VORTX at a dose of 80 mg/kg/daily/orally for three weeks with certain modifications [29].
6. **Rats exposed to VORTX high dose + RUT (G6)**: The included rats concurrently administrated VORTX at a dose of 80 mg/kg/daily/orally [29] and RUT at a dose of 25 mg/kg/daily/orally [27] for three weeks with certain modifications.

Twenty-four hours after the last experimental design dosage administration, the final rats' body weight for all the enclosed groups was directly weighted using automatic balance. Required blood samples were taken from rats' retro-orbital veins. Obtained blood was centrifuged for 10 min at 4℃-3500 rpm. The serum was further stored at -20℃ for the biological assessment. Immediately after the rat's decapitation under the effect of isoflurane anesthesia (2–3% in 100% oxygen) [30], the liver was isolated from each decapitated rat and directly washed with phosphate buffer saline. Whereas each liver was divided into two parts, the first part was for the preparation of the tissue homogenate according to the required biological assessment and manufacturer instructions, while the other part was fixed in 10% formalin and ethanol respectively for histopathological studies. Different isolated liver supernatant of the prepared liver tissue homogenate were stored for different assessments.

Serum biological assessment

Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Albumin (Alb), and Total Protein (TP) kits were regularly detected in the obtained serum from all groups according to Spectrum-Diagnostics (Cairo, Egypt) manufacturer instructions. Lactate dehydrogenase was estimated using UV spectrophotometry via following the decrease in NADH at 340 nm according to Berger [31] and Kjeld [32].

Detection of oxidative stress and antioxidants enzymes activities

Each isolated liver was directly homogenized in KCL buffer 1.15% (1:10) and then centrifuged at 1000xg (+4 C) for 15 min. MDA was detected in supernatants according to Placer et al. [33] and Mihara and Uchiyama [34] in correlation with the thiobarbituric acid reaction measured at 532 nm. Meanwhile, the homogenate for GSH analysis was centrifuged at 9,000 rpm xg and detected according to Sedlak and Lindsay [35] and Beutler et al. [36]. On the other hand, for the detection of SOD and GST, isolated liver parts were homogenized in KH_2PO_4 buffer + 1 mmol EDTA (pH 7.4) and then centrifuged at 12,000 xg for 30 min at 4 °C. The collected supernatant was used for the enzymatic and protein assessment. The Protein concentration was detected using standard Bovine serum albumin. SOD activity was detected according to Kakkar et al. [37], while GST phase II metabolizing enzyme was determined according to Habig et al. [38].

Determination of lysosomal enzyme activities (LEAs)

Lysosomal Enzyme Activities (LEAs) including Acid phosphatase (ACP), β- galactosidase (β-GAL), and β-N-acetyl glucosaminidase (β-NAG) were estimated and determined by spectrophotometry according to Van Hoof and Hers [39].

Detection of inflammatory and apoptotic factors

Capsase-3 and Cytochrome-C (Cyt-C) were detected and estimated in prepared liver tissue homogenate according to manufacturer instructions (MyBioSource). Meanwhile, Alpha-fetoprotein (AFP) was detected and estimated in serum according to manufacturer instructions (MyBioSource).

Estimation and detection of DNA damages

Detection of hepatic DNA fragmentation was estimated according to Wu et al. [40] and Trerè et al. [41]. DNA Ladder presence was detected according to Wlodek et al. [42]. Meanwhile, DNA extraction was conducted according to Aljanabi and Martinez [43]. Electrophoresis gel was prepared using agarose 2% containing (200 µg/ml) ethidium bromide 0.1%. Loading buffer (bromophenol blue 0.25%, xylene 0.25%, and glycerol 30%) was highly mixed with different DNA samples and was directly loaded into different wells (20 µl DNA per lane) with a special standard ladder marker. Whereas, the prepared gel was electrophoresed at a 50 mA/1.5 h estimated current using an electrophoresis machine. The DNA was visualized and photographed using UV light illumination. We wish to note that, due to technical constraints during the imaging process, full-length gel images were not obtainable for inclusion in this manuscript. However, it is essential to emphasize that the absence of these images did not compromise the integrity or validity of our results. The gel blot images presented in this study accurately reflect the findings obtained from our experiments. All relevant images, including additional gel blot images, have been provided as supplementary material accompanying this manuscript. Readers are encouraged to refer to the supplementary file for a comprehensive overview of the experimental data and procedures described in this study.

Table 1 The alleviative role of RUT against VORTX toxicity on organ and body weight

Groups	Body weight (g) Mean ± SE		Liver weight (g)
	Initial	Final	
Control Rats (G1)	$158.333 \pm 3.158^{\$}$	$268.833 \pm 7.586^{@}$	$1.921 \pm 0.020^{@}$
Rats exposed to RUT (G2)	$158.167 \pm 2.257^{\$}$	$264.833 \pm 5.594^{@}$	$1.935 \pm 0.020^{@}$
Rats exposed to VORTX low dose (G3)	$160 \pm 4.049^{\$}$	$200.833 \pm 3.360^{\$}$	$1.656 \pm 0.054^{\#}$
Rats exposed to VORTX low dose + RUT (G4)	$160.5 \pm 5.981^{\$}$	$240.666 \pm 3.480^{\#}$	$1.755 \pm 0.045^{@}$
Rats exposed to VORTX high dose (G5)	$165.5 \pm 6.026^{\$}$	$187.166 + 1.301^{\$}$	$1.186 \pm 0.052^{\#}$
Rats exposed to VORTX high dose + RUT (G6)	$164.666 \pm 5.713^{\$}$	$199 \pm 3.651^{\$}$	$1.41 \pm 0.051^{\#}$

Values are expressed as mean ± SE of 6 rats per group. Values with the same superscript symbols are non-significant at (P>0.05) RUT = Rutin, Vortioxetine = VORTX

Histological analysis of isolated liver tissue

Isolated liver tissues were first washed and then directly fixed in formalin solution 10% for 2 days. Fixed tissues were then dehydrated in a prepared graded series of ethanol. Different samples were stained with hematoxylin and eosin (H&E) followed by being examined under light microscopy. Detection of pathological changes was mainly based on the presence of hepatocellular necrosis, disarrangement of hepatic cells, and the degree of hepatic nuclear asymmetry.

Statistical analysis

Observed data are expressed in the form of mean ± standard error. Statistical analysis was conducted using a one-way analysis of variance, followed by Dunnett's test to assess the degree of statistical. $P<0.05$ level was considered statistically significant.

Results

Effect of Rutin (RUT) and Vortioxetine (VORTX) on the final body and liver estimated weights

Rats exposed to VORTX low (G3) and high doses (G5) showed a significant reduction in estimated body weight and liver size when compared to control (G1) and rats exposed to RUT (G2) ($P<0.05$). Meanwhile, body and liver organ weights were slightly restored following the exposure to RUT in both groups of rats exposed to VORTX high dose (G6) and VORTX low dose (G4) when compared to control (G1) and rats exposed to RUT (G2) ($P<0.05$), indicating the ameliorating effect of RUT against VORTX-induced hepatotoxicity as shown in (Table 1).

Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Albumin (Alb), Total Protein (TP), and Lactate dehydrogenase serum levels following the exposure to VORTX different doses and RUT treatment

Serum AST, ALT, and LDH levels were estimated and given as shown in (Fig. 1). The observed data demonstrated that the exposure to VORTX low (G3) and high doses (G5) resulted in a significant increase in the serum levels of AST, ALT, and LDH when compared to control (G1) and rats exposed to RUT (G2) ($P<0.05$). This indicates the degree and severity of hepatocytes damage, especially among group (G5). On the other hand, it was highly observed that serum albumin and total protein levels were significantly decreased following the exposure to both doses of VORTX (G3 & G5) with more relevant effects in the group of rats exposed to high VORTX dose

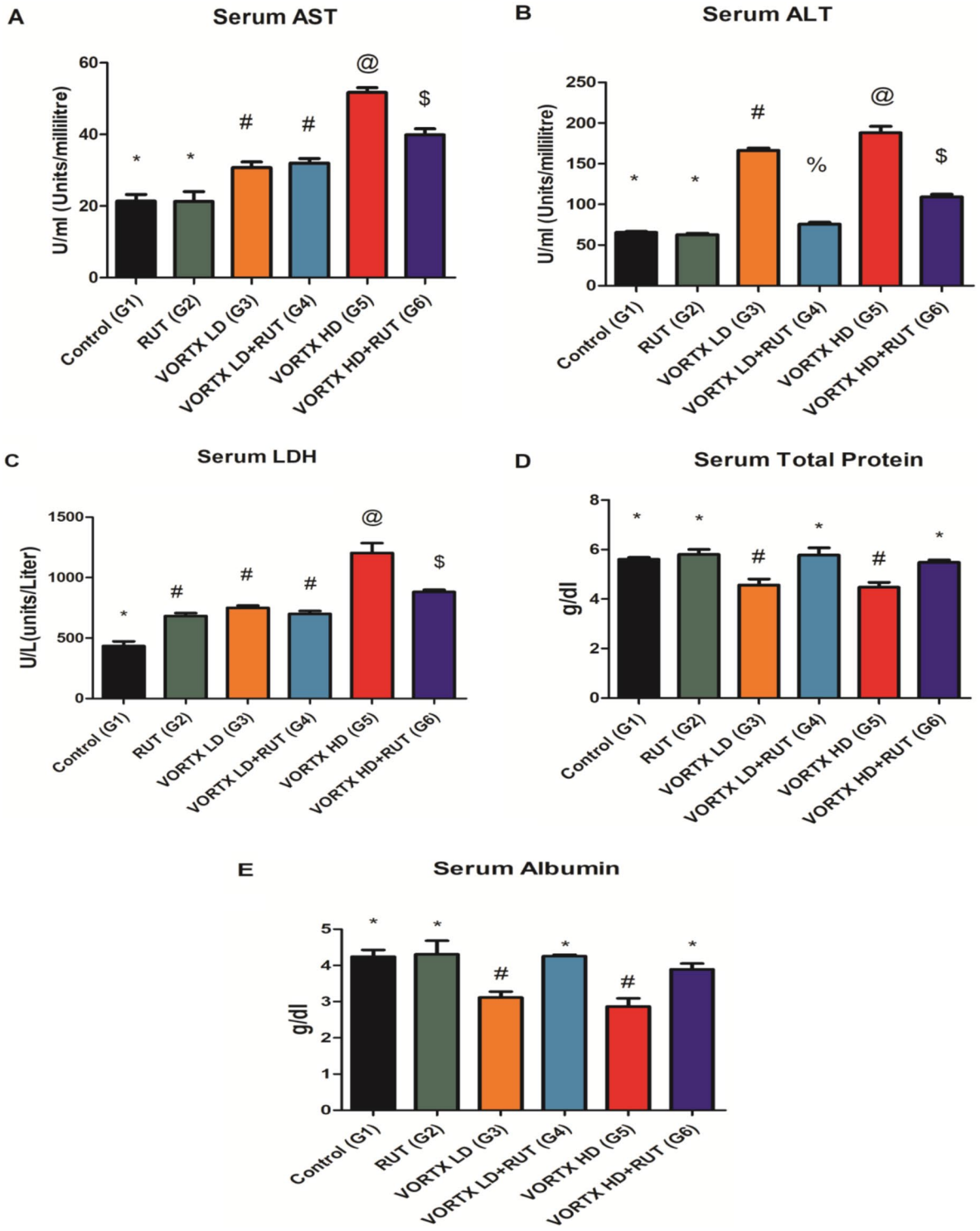

Fig. 1 The alleviative role of RUT against VORTX toxicity on (**A**) AST, (**B**) ALT, (**C**) LDH, (**D**) Total protein, and (**E**) Albumin levels among exposed rats. Values are expressed as mean ± SE of 6 rats per group. Values with the same symbols are non-significant at ($P > 0.05$) RUT = Rutin, Vortioxetine = VORTX, Low dose = LD, High dose = HD

(G5). However, it was demonstrated that administration of RUT in both groups of rats exposed to low (G4) and high VORTX doses (G6) protected the liver tissues from severe cellular damage by restoring adequate levels of AST, ALT, LDH, albumin, and total protein when compared to control (G1) and rats exposed to RUT (G2) ($P<0.05$) as shown in (Fig. 1).

Status of oxidative stress and antioxidant markers following the exposure to VORTX different doses and RUT treatment

In the current study, MDA, SOD, GST, and GSH levels were detected for the estimation of oxidative stress in liver tissues following the exposure to low and high doses of VORTX (G3&G5, respectively) as represented in (Fig. 2). According to our observed data, the administration of VORTX in low (G3) and high doses (G5) increased the MDA level in liver tissues and suppressed SOD, GST, and GSH activities in liver tissues when compared to control (G1) and rats exposed to RUT (G2) ($P<0.05$). Moreover, it was observed that RUT administration among both groups (G4 & G6) alleviated the induced oxidative stress and free radicles levels as a drawback of daily VORTX administration by decreasing MDA levels associated with increasing SOD, GST, and GSH liver tissue levels when compared to control (G1) and rats exposed to RUT (G2) ($P<0.05$) as shown in (Fig. 2). This emphasizes the fact that the daily VORTX administration has a significant damaging effect on the liver tissues by inducing oxidative damage to hepatocytes leading to severe hepatotoxicity.

Status of inflammatory and apoptotic markers following the exposure to VORTX different doses and RUT treatment

To evaluate the effects of VORTX misuse on the inflammatory markers, AFP was detected in serum while Cytochrome-C and Caspase 3 were detected in liver tissues. According to the obtained results represented in (Fig. 3), it was determined that the administration of VORTX in low (G3) and high doses (G5) resulted in elevated

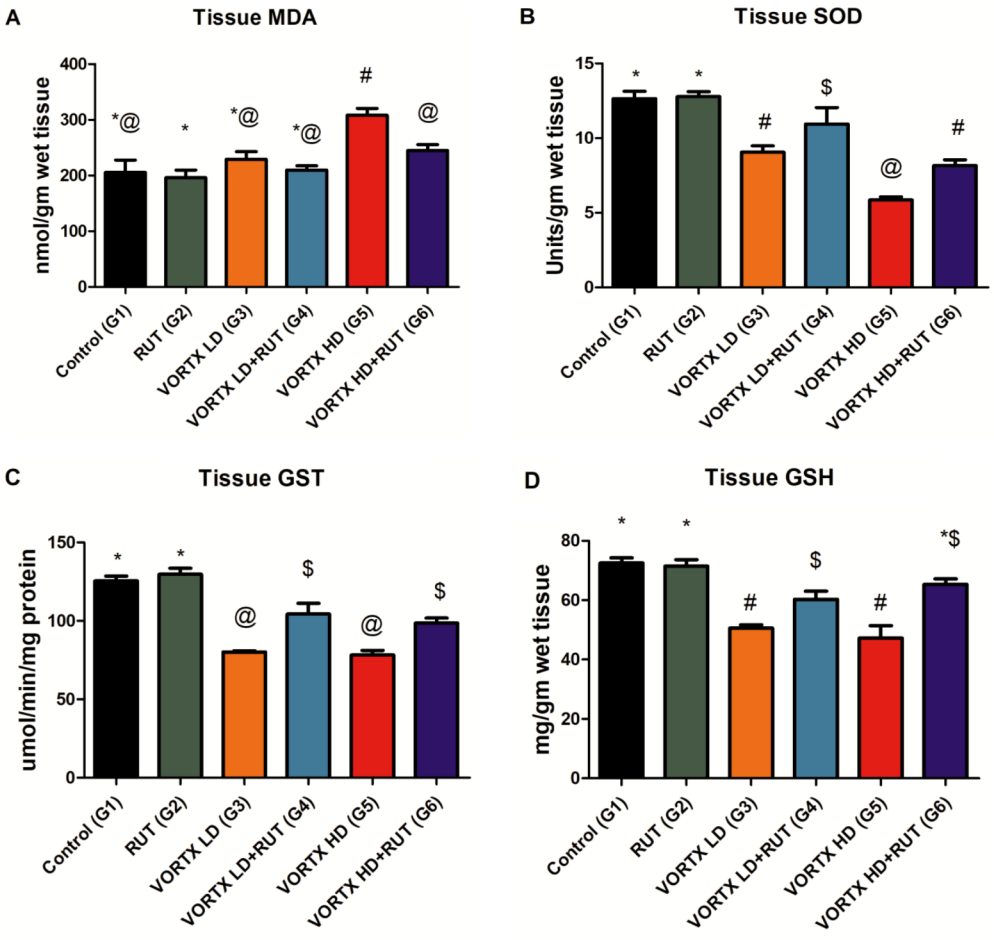

Fig. 2 The alleviative role of RUT against VORTX toxicity on (**A**) MDA, (**B**) SOD, (**C**) GST, and (**D**) GSH tissue levels among exposed rats. Values are expressed as mean ± SE of 6 rats per group. Values with the same symbols are non-significant at ($P>0.05$) RUT = Rutin, Vortioxetine = VORTX, Low dose = LD, High dose = HD

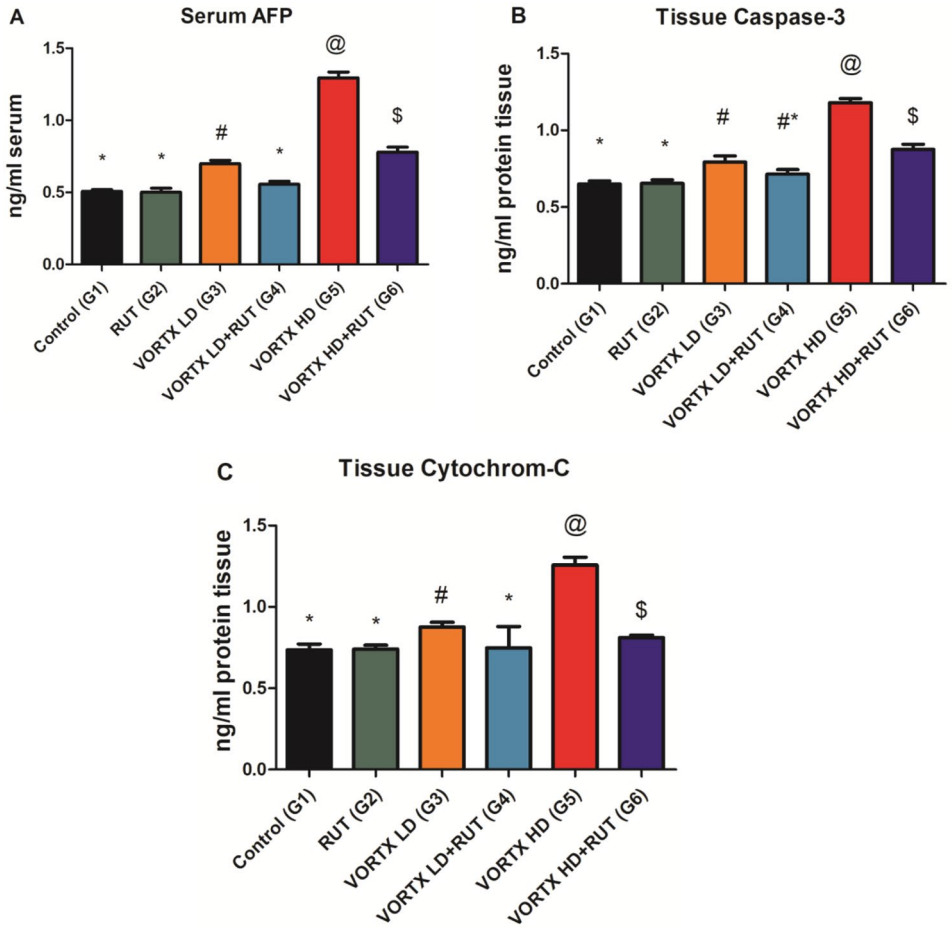

Fig. 3 The alleviative role of RUT against VORTX toxicity on (**A**) AFP, (**B**) Caspase-3, and (**C**) Cytochrome-C levels among exposed rats. Values are expressed as mean ± SE of 6 rats per group. Values with the same symbols are non-significant at ($P > 0.05$) RUT = Rutin, Vortioxetine = VORTX, Low dose = LD, High dose = HD

AFP, caspase 3, and cytochrome C levels among all the exposed group when compared to control (G1) and rats exposed to RUT (G2) ($P<0.05$). These observed results highlight the degree of inflammation and apoptosis induced as a drawback of VORTX daily administration among exposed groups, especially in high-dose VORTX group (G5). Whereas, the administration of RUT among rats exposed to VORTX in low and high doses (G4, G6 respectively) resulted in major improvement among all the inflammatory estimated parameters when compared to control (G1) and rats exposed to RUT (G2) ($P<0.05$) as shown in (Fig. 3).

Status of lysosomal enzymes activities (LAEs) following the exposure to VORTX different doses and RUT treatment

The effect of VORTX administration on the liver lysosomal enzyme activities represented in the form of (Acid phosphatase, B-NAG, and B-GAL) was demonstrated in (Fig. 4). It was concluded that VORTX administration, especially among the group of rats exposed to high VORTX dose (G5) significantly increased the release level and activities of these three enzymes when compared to control (G1) and rats exposed to RUT (G2) ($P<0.05$). The Administration of RUT significantly ameliorated the effect of VORTX on both low and high doses when compared to control (G1) and rats exposed to RUT (G2) ($P<0.05$) as shown in (Fig. 4).

DNA fragmentation analysis and purity following the exposure to VORTX different doses and RUT treatment

Table 2 illustrates the degree of DNA purity and the concentration of total dsDNA among all the exposed six groups of rats to estimate the degree of VORTX-induced hepatotoxicity and the alleviative role of RUT against the hepatic damage induced by daily VORTX administration at different pharmacological doses. The normal estimated DNA purity should be between (1.8 to 2.0) at the absorbance of (260 nm) indicating that nucleic acid (NA) is free from any contamination. As demonstrated in our observed data, DNA purity and total dsDNA concentration were detected to be decreased following the exposure to VORTX low dose (G3) and (G5) with a more

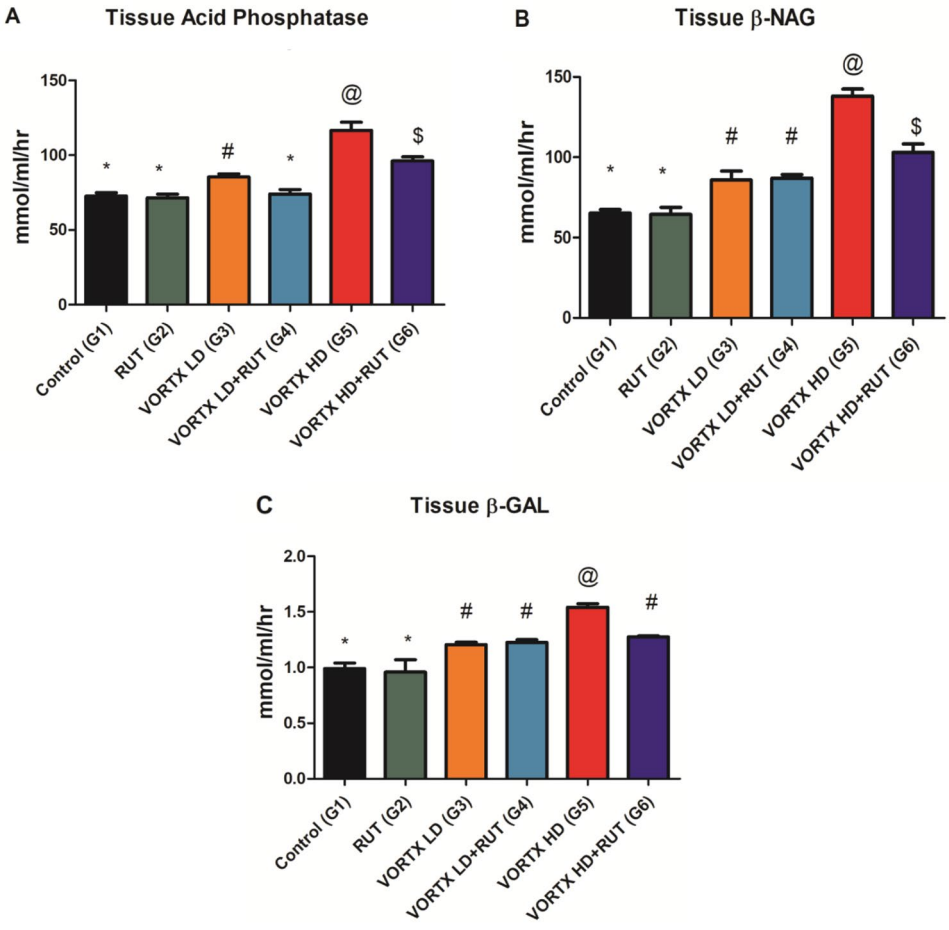

Fig. 4 The alleviative role of RUT against VORTX toxicity on (**A**) Acid phosphatase (**B**) B-NAG, and (**C**) B-GAL, levels among exposed rats. Values are expressed as mean ± SE of 6 rats per group. Values with the same symbols are non-significant at ($P > 0.05$) RUT = Rutin, Vortioxetine = VORTX, Low dose = LD, High dose = HD

Table 2 The alleviative role of RUT against VORTX toxicity on DNA purity and total ds DNA concentration in rats' liver tissues

Groups	Mean ± SE	
	Purity A260/A280	Total dsDNA Concentration (mg/ml)
Control Rats (G1)	$1.9216 \pm 0.0205^{@}$	$4.5566 \pm 0.0923^{@}$
Rats exposed to RUT (G2)	$1.9350 \pm 0.0202^{@}$	$4.5066 \pm 0.0899^{@}$
Rats exposed to VORTX low dose (G3)	$1.6566 \pm 0.0543^{\#}$	$4.025 \pm 0.0808^{\$}$
Rats exposed to VORTX low dose + RUT (G4)	$1.755 \pm 0.0452^{\#}$	$4.3216 \pm 0.1014^{@\$}$
Rats exposed to VORTX high dose (G5)	$1.1866 \pm 0.0520^{\$}$	$2.1666 \pm 0.1473^{\%}$
Rats exposed to VORTX high dose + RUT (G6)	$1.41 \pm 0.0516^{\%}$	$3.3216 \pm 0.1711^{\&}$

Values are expressed as mean ± SE of 6 rats per group. Values with the same superscript symbols are non-significant at (P>0.05) RUT = Rutin, Vortioxetine = VORTX

significant decrease among the high dose exposed group (G5). On the other hand, DNA purity and total dsDNA concentration were increased among both RUT-treated groups + VORTX low/High doses (G4 & G6, respectively) when compared to control (G1) and rats exposed to RUT (G2) ($P<0.05$). Moreover, the degree of DNA fragmentation was detected and estimated by gel electrophoresis technique represented in the form of DNA ladder constituting series of fragments (180–200 bp) as shown in (Fig. 5). An observed increase in the degree of DNA fragmentation was observed following the exposure to VORTX low (G3) and high doses (G5) with a more significant increase in the degree of fragmentation among the group of rats exposed to high VORTX dose (G6) when compared to control (G1) and rats exposed to RUT (G2) ($P<0.05$). Treatment with RUT resulted in a detected significant improvement in the degree of DNA fragmentation among (G4 & G6) when compared to control (G1) and rats exposed to RUT (G2) ($P<0.05$) as demonstrated in Table 2.

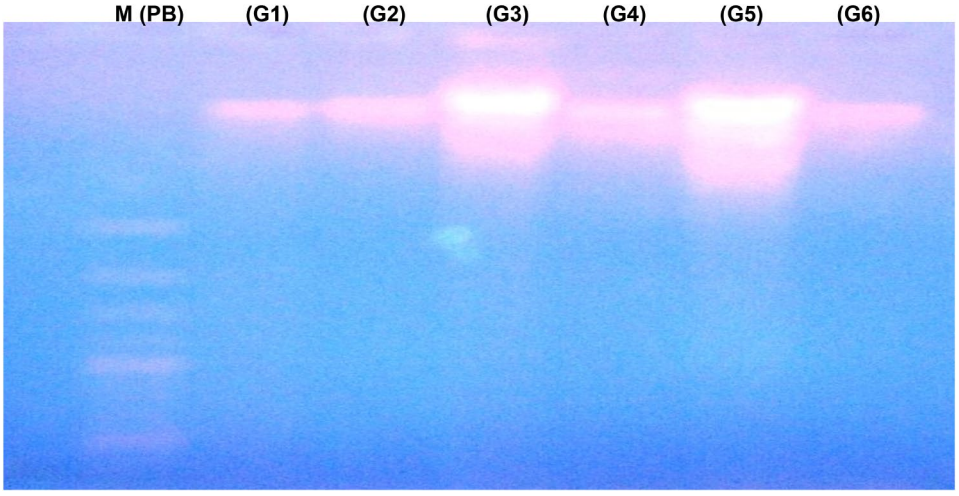

Fig. 5 The alleviative role of RUT against VORTX toxicity on DNA fragmentation of liver tissues among all exposed rats. Agarose gel electrophoretic isolated DNA pattern of liver tissues among all exposed rats. Lane 1 from Left: (Marker 2.5kbp), Lane 2: (control G1), Lane 3: (Rats exposed to RUT G2), Lane 4: (Rats exposed to VORTX low dose G3), Lane 4: (Rats exposed to VORTX low dose + RUT G4), Lane 5: (Rats exposed to VORTX high dose G5), and Lane 6: (Rats exposed to VORTX high dose + RUT G6)

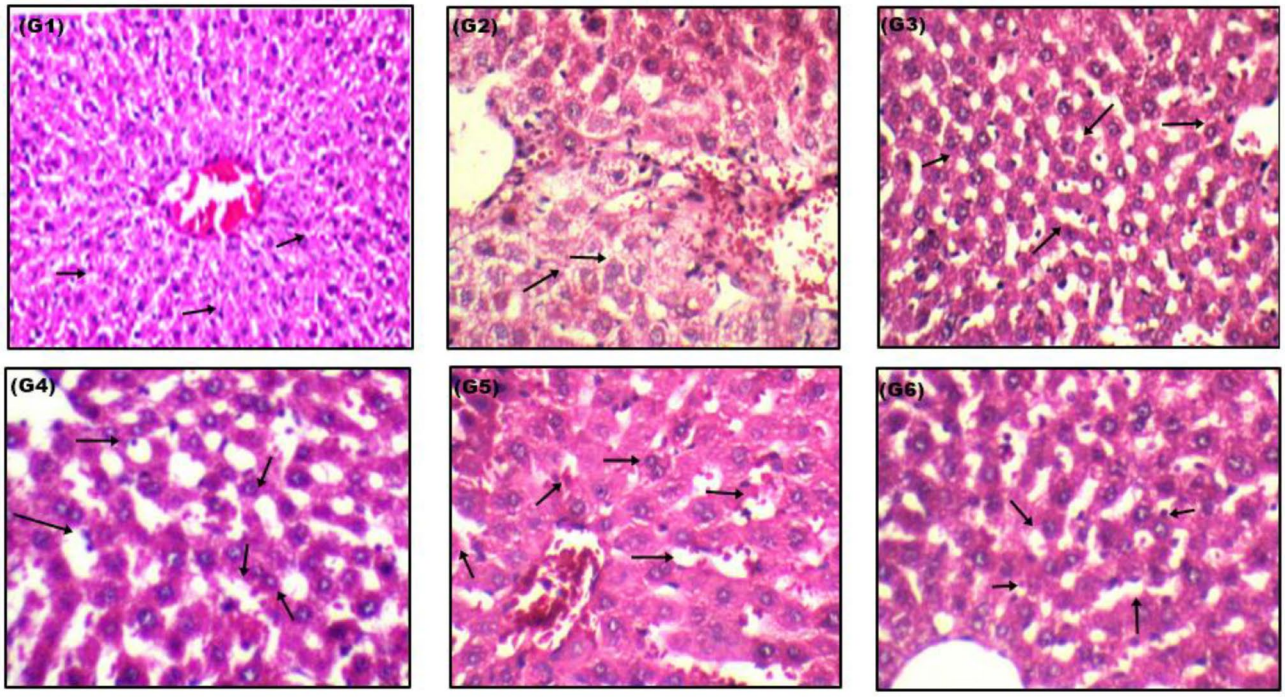

Fig. 6 Hematoxylin and eosin (H&E)-stained liver sections among all exposed groups (control G1): showed normal hepatocyte structures (400X), (Rats exposed to RUT G2): showing normal intact liver appearance (640X), (Rats exposed to VORTX low dose G3): showing inflammatory hepatocyte cells infiltration (640X), (Rats exposed to VORTX low dose + RUT G4): showing slight hepatocyte vacuolation and inflammation (640X), (Rats exposed to VORTX high dose G5): showing relevant congested, thickened and scattered portal/central veins (640X), and (Rats exposed to VORTX high dose + RUT G6): showing very slight hepatocyte vacuolation and mild degree of congested sinusoid (640X)

Histopathological structure

The light microscopic examinations of the isolated liver sections of the control (G1) (Fig. 6) showed normal hepatocyte structure with intact nucleus and cisternae of rough endoplasmic reticulum (RER). The isolated liver sections of the RUT exposed group (G2) revealed normal hepatocytes with intact and healthy Kupffer cells. However, the isolated liver sections of rats exposed to VORTX low dose (G3) showed hepatocytes with congested blood vessels along with extravasated RBCs. Swollen vacuolated hepatocytes were also detected around the central veins associated with aggregated fatty cells. Moreover,

congested dilated sinusoids with brown pigments were detected. The isolated liver section of the group of rats exposed to low VORTX dose+RUT (G4) showed mild inflammatory cell aggregates detected in some portal areas together with prominent Kupffer cells. Almost normal hepatocyte structures was detected with a limited number of vacuolated hepatocyte structures in focal areas. On the other hand, relevant congested, thickened, and scattered portal/central veins with proliferated bile ducts were detected among the group of rats exposed to VORX high dose (G5). Additionally, severe inflammatory aggregated cells, dilated congested sinusoids, and microvacuolated hepatocytes were also detected. Moreover, the isolated liver sections of rats exposed to high VORTX dose+RUT (G6) showed a relevant picture of regenerated normal hepatocytes. A mild degree of a congested sinusoid in limited areas was detected along with extravasated RBCs structure and very slight intact Kupffer cells. An improvement in the degree of aggregated inflammatory cells among different areas was also observed.

Discussion

Drug-induced hepatotoxicity and liver injury represent adverse reactions to the type of administrated drug and its metabolites, potentially leading to irreversible and prominent inadequacy in liver functions. These conditions encompass a wide range of manifestations and consequences, that range from asymptomatic abnormalities (silent stage) to symptomatic (severe symptoms and disabilities) [44]. Liver injury resulting from the drawbacks of drug abuse or misuse can be divided into two types: intrinsic and idiosyncratic. Intrinsic hepatotoxicity is dose-dependent, characterized by a short latency period, and follows a predictable disease time [45]. On the other hand, idiosyncratic hepatotoxicity is not dose-dependent, but exhibits variable manifestations, and has an unpredictable disease course [46]. The lack of specific biological markers often hinders early diagnosis of liver injury and hepatotoxicity. Clinical symptoms are diverse and may differ from one patient to another including loss of appetite, tiredness, fever, vomiting, jaundice, and muscle pain. In most cases, immediate treatment involves discontinuing the offending drug and providing the necessary required medical support [47].

The liver serves as the primary organ responsible for the metabolism of antidepressant drugs. Thus, it is important to find out how prolonged administration or overdoses of these administrated drugs, along with their metabolites, may impact this vital organ. Hepatotoxicity may directly result in severe inflammation, fibrosis, steatohepatitis, hepatic steatosis, cirrhosis, and necrosis [18, 19, 48]. Even at maintained therapeutic doses, prolonged or misuse of antidepressant drugs may result in serious hepatotoxicity [47, 49, 50]. It was previously highlighted in one of the clinical studies that the administration of antidepressants and psychotropic drugs was responsible for 7.6% of the induced liver injuries among 185 subjects [51, 52]. Therefore, it is important to establish an outline and strategy for prescribing antidepressant drugs to any patient, taking into consideration their hepatotoxicity and other associated risk factors, including diabetes and drug abuse [47, 50]. The metabolism of antidepressant drugs and SSRIs, including VORTX, occurs predominantly in the liver, via the cytochrome P450-dependent monooxygenase which serves as the main drug-metabolizing enzyme for a range of drugs such as steroids, xenobiotics, and vitamins. The lipophilic character of most antidepressant drugs facilitates their easy transfer to the cell membrane and is primarily metabolized in the liver [53].

The prolonged or high-dose administration of VORTX can lead to significant liver damage via different mechanisms, including direct hepatic toxicity, inflammation, apoptosis, oxidative stress, and DNA fragmentation, ultimately resulting in impaired hepatic function and structural alterations [54]. Oxidative stress and inflammation are the two main driving factors of hepatotoxicity and liver injury. As demonstrated in our results, the administration of VORTX in low and high doses results in an exaggerated increase in oxidative stress, and apoptotic factors in addition to a relevant decrease in antioxidants level. Consistent with our results, it was reported that the administration of VORTX and SSRIs induces oxidative stress and inflammation in the liver tissues by promoting apoptotic factors, ROS production, DNA damage, and lipid peroxidation, associated with suppressed oxidative stress release [54–57]. One of the main sources of elevated ROS in the liver is CYP450 and mitochondria in hepatocytes [58]. Additionally, Kupffer cells, immune cells, and neutrophils contribute to ROS production. ROS directly introduce carbonyl group compounds into several amino acid side chains, affecting DNA and protein structures and functions. Furthermore, Oxidative stress may directly oxidize polyunsaturated fatty acids type in the cascade of lipid peroxidation. ROS also results in DNA mutation, and a decrease in DNA purity and expression [59, 60]. This justifies that the misuse or prolonged administration of VORTX may directly lead to a direct reinforcement of DNA, which is likely an adverse consequence of triggered oxidative stress and the release of exaggerated inflammatory factors in affected liver tissues.

Meanwhile, the observed deficit in GSH release serves as a relevant indicator of the liver pro-oxidant state and the degree of hepatotoxicity [61]. Accordingly, the observed decrease in the level and the activity of GSH, GST, and SOD associated with an increase in MDA activity level along with apoptotic factors and

lysosomal enzymes, can be attributed to the administration of VORTX in both low and high doses. In agreement with our results [62–66], demonstrated that the administration of SSRIs resulted in a severe increase in oxidative stress and apoptotic factor levels in the liver tissue including caspase-3, Bax, AFP, and cytochrome-c, mediating severe damaging effects in hepatocytes. It was demonstrated in the current study the administration of VORTX resulted in a significant increase in liver function serum level biomarkers including AST and ALT along with LDH. On the other hand, a relevant decrease in the serum levels of albumin and total protein was also observed following the administration of VORTX especially in high doses. The elevation of these biomarkers indicates the degree of liver injuries and the state of hepatocyte damage. In accordance with our results, the administration of SSRIs resulted in severe liver injuries indicated by relevant elevation of liver function biomarkers in addition to relevant histopathological studies [62, 63, 65–70].

Interestingly, VORTX administration triggers substantial inflammatory responses as a drawback of elevated oxidative stress levels and ROS. The marked elevated levels in the inflammatory responses are reflected in the expression levels of caspase-3, cytochrome-c, and AFP. The increase in oxidative stress and ROS production directly affects membrane permeability and mitochondrial functions, resulting in server hepatocyte damage and initiating apoptotic cell death via different apoptotic pathways. These triggered apoptotic and inflammatory responses include toll-like receptors (TLR) and nuclear factor kappa B (NF-κB) [65, 66, 71, 72]. Consequently, the observed decrease in the DNA purity and total dsDNA concentration may be a consequence of increased ROS and oxidative stress in depression patients and those receiving antidepressants [65–67, 71, 56, 73, 74]. The detected histopathological alterations following the administration of VORTX, especially at high doses, including relevant inflammatory cell infiltrations, hepatocytes vacuolation, highly dilated sinusoids, and other several manifestations can be attributed to apoptosis, inflammation, and exaggerated oxidative stress.

Rutin, a flavonol compound which is abundantly found in different plants was demonstrated to have several pharmacological activities, including anti-inflammatory, antioxidant, vasoprotective, and cytoprotective [17, 75]. Flavonoids are majorly converted to different metabolites by the action of intestinal microflora and specific liver enzymes. Upon administration of rutin, it is actively converted to quercetin and other types of metabolites [27]. The hepatoprotective efficiency of RUT is evident through the notable reduction in liver enzyme activities, oxidative stress, apoptotic factors, DNA damage, and lysosomal enzymes induced by previous exposure to VORTX, especially at high doses [27, 76, 77]. Whereas, nearly normal levels of liver enzyme biomarkers, oxidative stress, antioxidants, inflammatory factors, total DNA, and histopathological studies were relevantly restored in RUT-treated groups pre-exposed to VORTX in both low and high doses. In line with our results, previous studies have demonstrated the hepatoprotective efficiency of RUT due to its various pharmacological properties, especially antioxidant, antiapoptotic, and anti-inflammatory [27, 73, 76, 77]. Since the administration of RUT restored the antioxidant and anti-inflammatory levels, relevant improvements in total dsDNA concentration and DNA purity levels were also detected in our observed levels. Meanwhile, the histopathological studies revealed that VORTX administration resulted in severe hepatic tissue damage supported by severe swelling, inflammation, and hepatocytes. These histopathological and pathological changes were restored following RUT administration indicating the relevant protective efficacy of RUT on liver morphology.

Conclusion

Since inadequate responses to prolonged or misused administration of antidepressants have been repeatedly seen due to various and unexpected side effects of drugs, new therapeutic approaches are urgently required. Our results reveal that the daily administration of Vortioxetine (VORTX) at both low and high doses can lead to varying degrees of liver injury and hepatotoxicity as a drawback of inflammation, elevated oxidative stress, apoptosis, and DNA damage. Importantly, our study demonstrates that Rutin (RUT) exhibits promising effects as a hepatoprotective agent in case administered as part of a daily routine. Rutin shows potential in mitigating VORTX-induced hepatotoxicity by restoring normal liver functions, reducing levels of ROS, alleviating inflammation, and suppressing apoptotic factors, all while bolstering the body's defenses against oxidative stress. The current study sheds new insights on the drawbacks associated with the daily administration of VORTX, particularly in relation to its hepatotoxic effects. Moreover, it emphasizes the positive impact of daily RUT flavone glycoside administration in counteracting the induced hepatic damage. Thus, these findings may influence clinical decision-making, especially in cases where VORTX is considered the drug of choice. Further clinical research should be effectively designed to assess the effectiveness of Rutin supplementation in preventing VORTX-induced hepatotoxicity.

In addition to the implications for clinical practice highlighted above, future research endeavors should aim to deepen our understanding of the hepatoprotective properties of Rutin and evaluate its potential utility in preventing antidepressant-induced hepatotoxicity.

Longitudinal studies are warranted to assess the long-term safety and efficacy of Rutin supplementation in mitigating VORTX-induced liver injury. Furthermore, comparative studies evaluating the safety profiles of various antidepressants and the impact of adjunctive therapies on hepatic function are essential for guiding treatment decisions and optimizing patient outcomes.

Abbreviations

VORTX	Vortioxetine
RUT	Rutin
SSRIs	selective serotonin reuptake inhibitors
MD	major depression
(MDDs)	major depressive disorders
LEAs	Lysosomal Enzyme Activities
RER	rough endoplasmic reticulum
TLR	toll-like receptors
NF-κB	nuclear factor kappa B

Supplementary Information

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Supplementary Material 1

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Author contributions
[MMA] and [IMIL] contributed to the study conception and design. Material preparation, data collection and analysis were performed by [MMA] and [IMIL]. [MMA] and [IMIL] estimated the whole biological parameters. The first draft of the manuscript was written by [MMA]. All authors read and approved the final manuscript.

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Data availability
The obtained data analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The conducted experimental design was approved by the Animal Research and Ethical Committee of the National Organization of Drug Control and Research (NODCAR) approval number (NODCAR/II/8/2023). All the conducted methods were carried out in accordance with the relevant guidelines and regulations and all methods were reported in accordance with ARRIVE guidelines. (Animal Research: Reporting of In Vivo Experiments).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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