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Mitigating effects of ginseng bulk on hepatic and immunological toxicity induced by boldenone undecylenate in rats

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ABSTRACT

Boldenone undecylenate (Bold) is an anabolic–androgen steroid, which is used illegally in veterinary and human uses for bodybuilding and fitness, but it is associated with adverse effects mainly to the liver and immunity. Ginseng has antioxidant and immune-modulatory activities. This study investigated the effect of ginseng bulk (Gin) on liver functions and the immunity of rats exposed to oxidative stress induced by using Bold. Forty healthy adult male Wistar Albino rats were equally divided into four groups; control, Sesame oil (vehicle control), Bold, and Bold + Gin 100 (100 mg/kg Gin). After 8 weeks, blood and liver samples were collected for analysis of liver enzymes (aspartate transaminase (AST), alanine transaminase (ALT), oxidative stress markers (catalase (CAT), malondialdehyde (MDA), immune markers (Immunoglobulin G (IgG)), and liver histology. The results showed that in the Bold treated group, AST, ALT, MDA, and IgG levels were significantly elevated, while catalase was reduced compared to the control group. However, the co-administration of ginseng bulk with Bold significantly improved these parameters, reducing liver enzymes, oxidative stress markers, and immune cell alterations while increasing hepatic catalase activity. Histological examination of the liver in the Bold group revealed severe damage, including necrosis, vacuolar degeneration, inflammation, and cirrhosis, while ginseng supplementation led to improvement in the liver architecture. In conclusion, ginseng bulk 100 has an ameliorating effect against the liver and the immune damage caused by Bold, highlighting their antioxidant and immune-modulatory properties.

Introduction

Anabolic-androgenic steroids (AAS) are synthetic hormones derived from testosterone (Tousson *et al*., 2013). Boldenone undecylenate (BOLD) (1,4-androstadiene-17b-ol-3-one) is one such anabolic steroid commonly used by athletes, bodybuilders, and racehorses to enhance physical performance and muscle growth. It does this by promoting positive nitrogen balance through stimulating protein synthesis, reducing protein breakdown, and aiding in water, nitrogen, and electrolyte retention (Ho *et al*., 2004; Oda and El-Ashmawy, 2012). Additionally, boldenone is used as a growth promoter to improve growth rates and feed conversion in livestock (Tousson *et al*., 2013). However, AAS use can lead to negative side effects, including disruptions to endocrine and immune systems, kidney damage, cardiovascular issues, and liver dysfunction (Hughes *et al*., 1995; Behairy *et al*., 2021). Since the liver is vital in drug metabolism, high doses of AAS often harm this organ (Frankenfeld *et al*., 2014), with hepatotoxicity associated with increased infiltration of neutrophils, lymphocytes, and eosinophils in the liver tissue (Bond *et al*., 2016). Bold may also pose direct risks to humans through injection and indirect risks from consuming meat from animals treated with Bold (Oda and El-Ashmawy, 2012).

Ginseng and its active component, ginsenosides, have been shown to provide beneficial effects across various health conditions, including those related to the reproductive, immune, endocrine, cardiovascular, and neurodegenerative systems (Shin *et al*., 2014; Hassan *et al*., 2024a, b). Researchers have extensively explored ginseng extracts and bioactive compounds due to their wide range of health-promoting properties, such as antioxidant, antitumor, antihyperglycemic, skin-protective, anti-osteoporotic, anticancer, anti-infective, and respiratory-relief effects (Riaz *et al*., 2019). Ginseng extracts have demonstrated protective effects on liver cells in vitro and against liver damage caused by various toxins, including hydrogen peroxide (H2O2) (Bak *et al*., 2012), alcohol (Park *et al*., 2012), aflatoxin B1, and fumonisins (Kim *et al*., 2011). Ginseng has also been shown to protect liver cells from radiation and viral hepatitis (Abdel-Wahhab *et al*., 2011).

Despite the widespread use of Gin in its bulk form, limited research has focused on its effects markedly in liver damage induced by Bold. This study aimed to investigate the potential antioxidant effects of bulk ginseng on liver enzymes and immune response in adult male rats. The investigation involved analyzing liver enzymes, assessing hepatic oxidative stress markers, measuring immunoglobulin G levels, and conducting histological examinations of the liver.

Materials and methods

Ethical approval

The study's protocols were approved by the Ethical Research Committee of the Faculty of Veterinary Medicine at Sohag University (Approval number: Soh.un.vetm / 00025 M.

Reagents

Korean Red Ginseng (100% natural Panax Ginseng Roots Powder) was obtained from IMTENAN Company, Assiut, Egypt. Boldenone undecylenate was sourced in its commercial form, Equi-gan® (Laboratorios Tornel Co., S.A., Mexico), with each vial containing an oily solution of 50 mg boldenone per mL. Sesame oil was procured from Chemajet Company, located in the second industrial area of Borg El Arab City, Alexandria, Egypt.

Animals

Forty adults male Wistar albino rats, weighing 240-260 g, were obtained from the Lab Animal House at the Faculty of Medicine, Sohag University. The rats were acclimatized for one week in clean, pathogen-free metal cages at the Physiology Department, Faculty of Veterinary Medi-

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cine, Sohag University. They were kept under a 12-hour light/dark cycle, with a temperature of 23±2°C, humidity levels of 50-55%, and provided with free access to standard rodent food and water (Basuony *et al*., 2020).

Experimental Design

Forty rats were randomly divided into four groups, with 10 animals in each group:
Group I (Control): Received 1 mL of distilled water orally once a day.
Group II (Sesame Oil Group): Received an intramuscular injection of 0.25 mL/kg BW of sesame oil (as a vehicle) once a week for eight weeks (Behairy *et al*., 2021).
Group III (Bold-treated Group): Received an intramuscular injection of 5 mg/kg BW of boldenone once a week for eight weeks (Behairy *et al*., 2021).
Group IV (Bold+ Gin 100 Group): Received 100 mg/kg BW of Korean red ginseng root powder orally via a drenching tube daily (Hassan *et al*., 2024 a& b), in addition to an intramuscular injection of 5 mg/kg BW of boldenone once a week for eight weeks (Behairy *et al*., 2021).

Body weights were measured weekly to adjust doses, and administrations began at 9:00 AM each day.

Samples collection

Blood samples collection

At the end of the experiment, the rats were sedated with an intraperitoneal injection of sodium thiopental (50 mg/kg BW). Blood samples were drawn from the retro-orbital venous plexus of each group, and were collected in tubes without anticoagulant, allowed to clot, and then centrifuged at 3000 rpm for 15 minutes. The separated serum was stored in Eppendorf tubes at -80°C for liver enzymes and immunoglobulin G analysis.

Liver samples collection

Rats were euthanized, then the liver was removed and preserved in 4% neutral buffered paraformaldehyde for histological analysis.

Liver enzymes assays

The frozen serum samples were thawed to measure liver enzymes, including Alanine aminotransferase (ALT) (Catalogue No. 265001) and Aspartate aminotransferase (AST) (Catalogue No. 261001). The enzyme assays were conducted using Spectrum kits (The Egyptian Company for Biotechnology (S.A.E), Cairo, Egypt), following the manufacturer's protocol (Breuer, 1996), and readings were taken at a wavelength of 340 nm using a microplate reader (Infinite 50, Mannedorf, Switzerland).

Evaluation of hepatic oxidative stress markers

A portion of the liver from each rat was homogenized in cold phosphate-buffered saline (PBS, 0.01 mol/L, pH 7.4) at a ratio of 1:9 (W/V) using a glass homogenizer. The homogenates were then centrifuged at 4000 rpm for 15 minutes, and the supernatants were collected in Eppendorf tubes for further analysis and kept on ice. Catalase (CAT) and malondialdehyde (MDA) levels in the liver homogenates were determined using reagent kits from Bio-diagnostic Co., Egypt, based on the methods of Aebi (1984) and Ohkawa *et al*. (1979), respectively, and using T70 UV/VIS spectrophotometer.

Immunoglobulin G (IgG) Detection

Immunoglobulin G (IgG) is measured by using the Chemistry analyzer model Cobas 501 (F. Hoffmann-La Roche Ltd, Basel, Switzerland).

Histological examination of the liver

Liver specimens from the experimental groups were carefully dissected and immediately fixed in 4% neutral buffered paraformaldehyde (PFA). The organ samples were then dehydrated using increasing concentrations of alcohol, followed by clearing with xylene. They were processed through the conventional paraffin embedding method and sectioned at a thickness of 5 µm. The sections were floated in a warm water bath to adhere to slides, dried in an oven at 50-55°C, and stained with Hematoxylin and Eosin (H & E) for standard histological evaluation under a light microscope (Mayada *et al*., 2015).

Morphometric study

The section samples were scored semi-quantitatively depending on the visual field inspection of 10 sections from each group. Photographs of liver tissues were taken, and the cellular alterations were counted in 10 random areas (each 1 mm^2) at a magnification of 40× (Monmeesil *et al*., 2019). Organ histology analysis was carried out by giving a score based on the level of damage seen in each group severity in the examined tissue: 0 = no lesions; 1 = mild (1 to 25%); 2 = moderate, (26 to 45%); 3 = severe (> 45%) as described previously (Gibson-Corley *et al*., 2013; Hamdin *et al*., 2019)., and then the scores were added to create a final total lesion score ranging from 0 to 12 for liver tissue (Meyerholz and Beck, 2020; Barakat *et al*., 2023). Liver tissue sections were scored according to alterations in hepatocytes, inflammation, vascular changes, and portal areas. Morphometry was carried out at the Image Analysis Unit, Department of Pathology and Clinical Pathology, Faculty of Veterinary Medicine, Sohag University.

Statistical analysis

The collected data were statistically analyzed using GraphPad Prism 8 (GraphPad Software, San Diego, California, USA). Results were presented as mean ± standard error of the mean (SEM), and group differences were assessed using one-way analysis of variance (ANOVA). When significant differences were found, means were compared using Tukey's test. A p-value of less than 0.05 was deemed statistically significant when compared to the control group (Brown, 2005). Regarding morphometrical lesion scores. Data are expressed as means ± standard deviations. Significant differences between groups were marked by different asterisks through the Kruskal-Wallis test with Dunn's Multiple Comparison post hoc test: *$p \leq 0.05$, *** $p \leq 0.001$).

Results

Effect of ginseng bulk on boldenone- induced increase on liver enzymes levels

The obtained results revealed a significant increase ($p < 0.05$) in alanine aminotransferase and aspartate aminotransferase levels in rats that received BOLD and Bold+ Gin100 compared with their control and sesame oil groups. However, there was a significant decrease ($p < 0.05$) in rats that received Bold+ Gin100 compared with rats that received Bold (Table 1).

Effect of ginseng bulk form on boldenone-induced disturbance on hepatic Oxidants/Antioxidants status

As presented in Table 2, the administration of boldenone caused a significant increase ($p < 0.05$) in hepatic MDA level compared with the control and sesame oil groups. However, rats treated with Bold showed a significant decrease in the hepatic level of CAT compared with control and sesame oil, and there were non-significant changes between all other

treated groups and their control group. While Bold+ Gin100 administration for eight weeks to adult male rats significantly ($p < 0.05$) reduced MDA level and elevated the level of CAT in the hepatic tissues relative to Bold- treated rats.

Table 1. Liver enzymes in control and treated rats after administration with Gin (50 and 100) mg / kg BW for 60 days.

Group	Alanine aminotransferase (U/l)	Aspartate aminotransferase (U/l)
Control	5.55 ± 0.34	14.65 ± 1.14
Sesame oil	5.82± 0.33	15.02 ± 0.58
Bold	15.90± 0.89 *#	35.59± 2.55 *#
Gin 100+ Bold	11.18±0.83 *#$	23.39± 2.47 *#$

n = 10, values are expressed in mean ± S.E.M. * $p \leq 0.05$ compared with control, # $p \leq 0.05$ compared with sesame oil and $ $p \leq 0.05$ compared with Bold.

Table 2. Levels of Liver Malondialdehyde (MDA) (nmol/g tissue), and catalase (CAT) (U/g tissue)} in control and treated rats (mean ±SE).

Group	Malondialdehyde (MDA)	Catalase (CAT)
Control	17.16± 1.38	1.03±0.01
Sesame oil	15.25±0.65	1.05±0.08
Bold	30.96±1.54*#	0.47±0.04*#
Gin 100+ Bold	20.12±2.01 $	0.83±0.09 $

n = 10, values are expressed in mean ± S.E.M. * $p \leq 0.05$ compared with control, # $p \leq 0.05$ compared with sesame oil and $ $p \leq 0.05$ compared with Bold.

Effect of ginseng bulk form on boldenone- induced increase of immunoglobulin G (IgG) (mg/dl) level

As shown in Table 3, the immunoglobulin G level exhibited a significant increase ($p < 0.05$) in the boldenone group compared to the control and sesame oil groups. while there were non- significant differences in all other groups compared with their control. Conversely, there was a significant decrease ($p < 0.05$) in the Gin100+ Bold group compared to the Bold group.

Table 3. Levels of immunoglobulin G (IgG) (mg/dl) in control and treated rats for 60 days.

Group	Immunoglobulin G (mg/dl)
Control	200.40±18.80
Sesame oil	204.60±12.71
Bold	467.10±41.46*#
Gin 100+ Bold	303.00±20.07$

n = 10, values are expressed in mean ± S.E.M. * $p \leq 0.05$ compared with control, # $p \leq 0.05$ compared with sesame oil and $ $p \leq 0.05$ compared with Bold.

Histopathological assessments

The liver tissue section from the control group showed normal histological architectures presenting a normal central vein and hepatocytes arranged in cords separated by normal sinusoids. The portal triad showed a normal portal vein, hepatic artery, and bile duct (Figure 1 A and B). Besides, the liver tissue section from the sesame oil-treated rats was similar to the control group (Figure 1C, D). However, the liver tissue section from the Bold group showed marked histopathological alterations, including a congested and dilated central vein with detached endothelial lining, necrotic hepatocytes characterized by karyolytic nuclei and ghost cell appearance, and vacuolar degeneration in hepatocytes. Kupffer cell activation around the portal area, necrotic megalocytes, coagulative necrosis, and focal necrosis (loss of hepatocytes replaced by inflammatory cells) were observed. Other findings included congested and dilated sinusoids, bile pigment deposition, hepatic cirrhosis with fibrous bridges between portal areas, biliary fibrosis (confined around the portal vein), and bile duct hyperplasia with ductal proliferation forming irregular and tortuous channels in the portal and periportal regions (Figure 1E, F). Bold+ Gin 100- -treated group showed marked improvement in the histological alterations compared to the Bold group. The observed findings included a mild congested central vein, dilated and congested hepatic sinusoids, mild vacuolar degeneration in hepatocytes, and mild Kupffer cell activation. The portal triad showed a mild congested portal vein, periportal fibrous connective tissue proliferation, and mononuclear inflammatory cell infiltration (Figure 1G, H). The histomorphometric analysis of the liver tissue lesions is presented, showing the total lesion scores recorded in the examined groups. The results indicate a significant increase in the lesion scores in the Bold group ($p \leq 0.0001$) and the Bold+100 Gin group ($p \leq 0.05$) when compared to the control group, and a significant improvement in the Bold group treated with 100Gin compared with Bold untreated group (Figure 2).

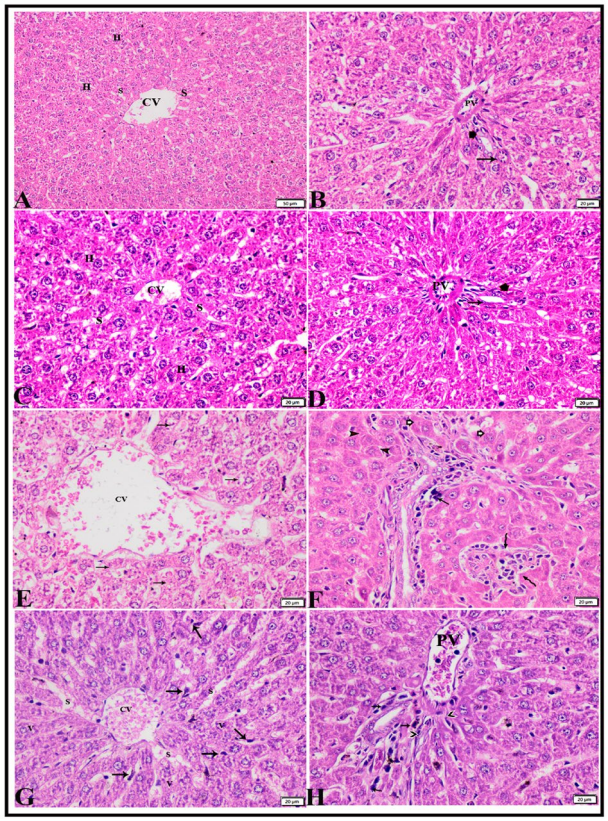

Figure 1. Photomicrograph of the liver in control and treated rats. (A): The control group showed normal histological architectures: normal central vein (CV) and normal hepatocytes (H), with in-between normal sinusoids (S). (B): normal portal tirade: normal portal vein (PV), normal hepatic artery (thin arrow) and normal bile duct (arrowhead). (C): The liver tissue section from the sesame oil-treated group showed normal hepatic architectures: a normal central vein and normal hepatocytes arranged in cords, with in-between normal sinusoids. (D): normal portal tirade: normal portal vein, hepatic artery (arrowhead), and normal bile duct (thin arrow). (E): The liver of rats administrated the boldenone showed: a congested and dilated central vein with detached endothelium lining, necrotic hepatocytes (arrows) (karyolitic nucleus with ghost cellular appearance). (F): Kupffer cell reaction around the portal area (thin arrow), necrotic megalocytes (white arrowheads), coagulative necrosis of hepatocytes (red arrowheads), focal necrosis; several adjacent hepatocytes are absent and replaced by inflammatory cells (zigzag arrows). (G): Liver of rats from Gin 100+ Bold - treated group showing: congested central vein, dilated and congested hepatic sinusoids, mild vacuolar degeneration in hepatocytes, mild Kupffer cell reaction (arrows). (H): portal triad showing: congested portal vein, periportal fibrosis connective tissue proliferation (arrowheads), mononuclear inflammatory cellular infiltration (arrows).

Discussion

Limited studies investigated the effects of ginseng bulk on various physiological processes. Therefore, this study aimed to evaluate the potential impact of ginseng bulk on liver function and immunity in adult male rats, including those exposed to oxidative stress induced by boldenone undecylenate.

The present study's findings reveal that boldenone treatment significantly elevated ALT and AST activities compared to the control and sesame oil groups, indicating its detrimental effects on liver function. These results are consistent with Neamat-Allah (2014), who reported a signif-

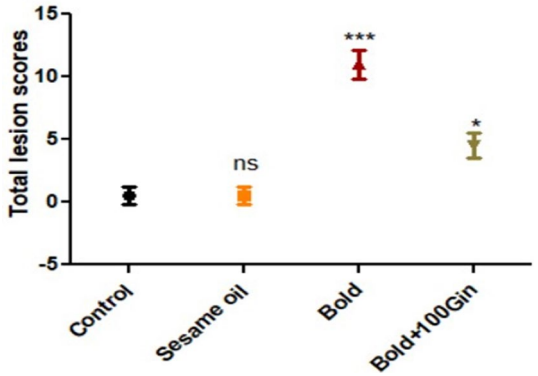

Figure 2. The histomorphometry graph showed the total lesion scores recorded in the examined liver tissue: a significant increase in the lesion score in Bold and Bold+100 Gin ($p \leq 0.0001$, and $p \leq 0.05$ respectively) compared with the control group.

icant increase in serum ALT and AST activities in the boldenone-treated group compared to the control, highlighting the adverse effects of androgenic steroids on liver function. Furthermore, studies by Niedfeldt (2018); Al-Desoki *et al.* (2019) and Sekuła *et al.* (2020) indicated that elevated levels of these enzymes in the bloodstream are indicative of liver cell damage or increased permeability of liver cell membranes.

In contrast, the present study demonstrated a significant reduction in ALT and AST levels in the group treated with 100 mg/kg of ginseng combined with boldenone, compared to the group treated with boldenone alone.

This indicates that administering ginseng at a dose of 100 mg/kg can mitigate the adverse effects of boldenone. These findings align with those of Huu Tung *et al.* (2012), who demonstrated that Ginsenoside Rg1, a key bioactive compound in ginseng, effectively reduced liver fibrosis in rats induced by thioacetamide by lowering fibrotic markers such as ALT and AST. Additionally, Ginsenoside Rg1 significantly inhibited cell growth, activation, and reactive oxygen species production in cultured liver stellate cells. Further evidence from Lee *et al.* (2005); Kim *et al.* (2016) and Kim (2016) supports the hepatoprotective effects of ginseng extract and its saponins.

The findings of this study indicate a significant increase in MDA level in the group treated with boldenone compared to the control and sesame oil groups, along with a notable decrease in CAT levels in the Bold - treated group relative to the control.

These results highlight the oxidative effects associated with Boldenone. This aligns with the observations of El-Moghazy *et al.*, (2012) who reported increased MDA concentrations in the boldenone group, suggesting that boldenone treatment induces oxidative stress in the liver, as evidenced by elevated levels of MDA, superoxide dismutase (SOD), and glutathione (GSH). Such changes indicate disruptions in oxidative stress markers and the antioxidant defense system in rabbits injected with boldenone.

Further support comes from Neamat-Allah, (2014); Behairy *et al.*, (2021) and El-Gharbawy (2024) who noted a marked increase in MDA level and a significant decrease in antioxidant markers in the boldenone-treated group compared to controls. The reduction in antioxidant enzyme activity may result from the conversion of free radicals into inactive compounds or direct inhibition of enzyme function by boldenone.

The present study demonstrated a significant decrease in MDA level and a notable increase in CAT levels in the group treated with Gin100+ Bold compared to the Bold group. This suggests a compensatory effect of ginseng at this dosage.

These findings align with those of Bak *et al.* (2012) and Park *et al.* (2021) who reported that ginseng possesses antioxidant properties by enhancing the function of natural antioxidant enzymes and directly neutralizing reactive oxygen species (ROS) and free radicals. Additionally, Ghamry *et al.*, (2022) noted that the antioxidant benefits of ginseng have long been recognized for its ability to enhance the activation of genes responsible for antioxidant enzymes that eliminate harmful ROS, thus boosting the activity of antioxidant enzymes and aiding in the removal of free radicals.

The histological findings of the liver in the Bold - treated group revealed significant damage, including congested and dilated central veins, necrotic hepatocytes with karyolytic nuclei, vacuolar degeneration, coagulative necrosis, and inflammatry cell infiltration. These findings are in line with Sabra *et al.* (2018) who also observed focal necrosis, central vein dilation, fatty changes, and inflammation in rats treated with boldenone. Similarly, Alfakje and Al-Mashhadane (2024) reported vascular degeneration and vacuolar changes, and Vasavan *et al.* (2020) noted that nandrolone decanoate injections caused cellular damage due to reduced antioxidant capacity.

In contrast, the liver tissue from the Gin100+ Bold groups showed milder changes, such as congested central veins, mild vacuolar degeneration, and some inflammation, with largely normal hepatocytes. These improvements are consistent with previous studies on ginseng extract. Hu *et al.* (2017) found that black ginseng reduced liver apoptosis caused by acetaminophen, and Ghamry *et al.*, (2022) reported that ginseng reduced microscopic liver damage caused by malathion exposure due to its antioxidant properties.

The results of the present study revealed a significant increase in IgG levels in the Bold- treated group compared to the control and sesame oil groups. This suggests that boldenone stimulates an immune response, as evidenced by increased IgG production. Limited studies have explored the effect of ginseng extract on IgG production with boldenone. Bertozzi *et al.* (2019) noted that chronic use of AASs can lower serum immunoglobulin levels, particularly IgG. Similarly, Flachi *et al.* (2018) highlighted that long-term AASs abuse, combined with a high-protein diet, can lead to reduced IgG and IgM levels, possibly causing nephrotic syndrome.

In contrast, the study showed a significant decrease in IgG levels in Gin 100+ Bold group compared to the Bold group. This indicates that ginseng bulk may mitigate boldenone's impact on the immune system by reducing IgG production.

To the best of the author's knowledge, no previous studies have specifically investigated the effects of ginseng bulk on IgG production concerning boldenone, establishing this study as a novel contribution to the field.

Conclusion

Ginseng bulk whole particles with a dose of 100 mg/kg BW induce a potent protective action in rat's hepatic and immunity disorders produced by boldenone undecylenate through its antioxidant and immune-modulatory activities.

Conflict of interest

The authors have no conflict of interest to declare.

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