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Crinum glaucum A. Chev bulb: Modulation of endogenous antioxidant enzyme in an animal-induced oxidative stress model

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ABSTRACT

Background & Aim: The mechanism of action of *Crinum glaucumbulb* (Cgb) A. Chev (Amaryllidaceae) is enigmatic. Therefore, this study aimed at investigating the possible modulating properties of an aqueous extract of Cgb on endogenous antioxidant enzymes during lipopolysaccharide (LPS)-induced oxidative stress in a rat model.

Experimental: 25 male and 25 female rats were divided into five groups (n=5) each: control group; treatment group, rats were given an aqueous extract of Cgb for 7 days; induced-oxidative stress group, rats were injected with LPS for 4 hours; post-Cgb group, rats were injected with LPS for 4 hours and treated with an aqueous extract of Cgb; and pre-Cgb group, rats were given an aqueous extract of Cgb for 7 days, injected with LPS for 4 hours, and treated with an aqueous extract of Cgb for 7 days. The blood, brain, heart, lungs, liver, and kidneys were harvested for the biochemical analysis. The endogenous antioxidant enzymes (catalase, superoxide dismutase, and glutathione-S-transferase) were analysed spectrophotometrically.

Results: The hallmark of LPS is its ability to decrease the activity of oxidative stress marker enzymes, as observed in this study. The pre- and post-administration of an aqueous extract of Cgb significantly ($P \leq 0.05$) reversed the damaging effect of LPS by increasing the activities of catalase and superoxide dismutase in the blood and organs of male and female rats, respectively, while plasma glutathione-S-transferase activity was inhibited.

Recommended applications/industries: The aqueous extract of Cgb has modulating properties to reduce the action of LPS-induced oxidative stress on endogenous antioxidant enzymes in male and female rats.

1. Introduction

In bacteria-host interactions, lipopolysaccharides (LPS) play a crucial role by modulating responses of the host immune system (Mohammad, 2021; Berta and Ruiz, 2018; Ajuwon *et al.*, 2014), triggering the production of pro-inflammatory mediators, which may result in a harmful condition known as oxidative stress (Halawa *et al.*, 2018;Sies, 2015). When free radicals (pro-oxidants) exceed antioxidant defences in the body, oxidative stress results, causing damage to crucial components like lipids, proteins, and DNA (Alwaleedi, 2016; Rahal *et al.*, 2014; Noworyta-Sokołowska *et al.*, 2013). Oxidative stress results from the accumulation of reactive oxygen species (ROS) in the cells and tissues, thereby altering the normal body homeostasis and

leading to the development of various diseases, which may involve alterations in the antioxidant defense systems (enzymatic or non-enzymatic) such as catalase, superoxide dismutase, glutathione-S-transferase, vitamin C, A, and E, among others (Salehi *et al.*, 2020; Stefanov *et al.*, 2020; Ogunrinola *et al.*, 2016; Pizzino *et al.*, 2017; Alam *et al.*, 2013).

Due to the broad accessibility and availability of medicinal plants among households and communities and the existence of bio-effective components including polyphenols, tannins, glycosides, and alkaloids, *inter alia*, it has been suggested as a prospective approach for the development of health-promoting agents (Ajuwon *et al.*, 2014; Xu *et al.*, 2022). An aqueous extract of the *Crinum glaucum* bulb (Cgb) plant (called river lily, stringlily, swamplily, *crinum* lily, and spider lily) is used in traditional medicine for the treatment of convulsions, cough, asthma, malaria, and sexually transmitted diseases, among others (Tian *et al.*, 2021; Umar *et al.*, 2021; Akintola *et al.*, 2013). Previous pharmacological studies have shown that the aqueous extract of this plant has therapeutic effects on lipid dysfunction, analgesic, anti-inflammatory, and anti-allergic activities (Ogunrinola *et al.*, 2022a; Cahlíkova *et al.*, 2019; Donald *et al.*, 2018; Refaat *et al.*, 2013; Houghton *et al.*, 2004). To uncover the mechanism of action of the preventive effect of the aqueous extract of *Crinum glaucum* bulb, this study was designed to investigate its effect on oxidative stress marker enzymes of endotoxin-induced oxidative stress in male and female rats.

2. Materials and Methods

2.1. *Plant collection and aqueous extraction*

One kilograms of *Crinum glaucum* bulb (Cgb) material was purchased at a local market at the Iyana-iba axis of Ojo Local Government Area, Lagos State, Nigeria, in February 2022, authenticated at the Department of Botany, Faculty of Science, Lagos State University, Ojo, Lagos State, Nigeria, and deposited in the herbarium (LASU/16879). The bulbs were trimmed to remove root hair, rinsed in water, drained of excess water, and then weighed. The bulbs were cut into pieces and soaked in distilled water for 72 hours in a plastic container. The crude aqueous extract of Cgb was collected through filtration and stored in the refrigerator for further use.

2.2. Acute toxicity test

The acute toxicity test was carried out by determining the median lethal dose (LD_{50}) using the limit dose test of Erhirhie *et al*. (2018), as modified by Adu *et al*. (2021) and Ogunrinola *et al*. (2022b) procedures via oral route. Briefly, eighteen rats were assigned equally to six well ventilated plastic cages (n=3). The 6 groups were given crude aqueous extract of Cgb orally at various dosage levels of 50 mg/kg, 100 mg/kg, 200 mg/kg, 400 mg/kg, 800 mg/kg and 1000 mg/kg body weight for 72 hours.

2.3. Experimental animal design and administration

Twenty five male and 25 female albino rats, weighing between 100 and 200 g, were acclimatized under well-aired standard housing conditions(temperature: 28–31^{0}C; photoperiod: 12 hours of natural light and 12hours of darkness; humidity: 50–55%) for 14 days. All the animals were fed a standard diet and water in the animal house of the Department of Biochemistry, Faculty of Science, Lagos State University, Ojo, Lagos State, Nigeria. The rats were divided into five groups (n=5) for male and female. In Group 1, rats were given water and animal feed only to serve as controls. Group 2 (treatment group) rats were administered 1000 mg/kg body weight of an aqueous extract of Cgb for 7 days (for a clinically meaningful effect). Group 3 (induced-oxidative stress group) rats were administered 4 mL/kg body weight of LPS for 4 hours, based on Olatunji *et al.* (2023) method. Group 4 (post-aqueous extract of Cgb group) rats were administered 4 mL/kg body weight of LPS for 4 hours and 1000 mg/kg body weight of an aqueous extract of Cgb for 7 days . In Group 5 (pre-aqueous extract of Cgb group), rats were administered 1000 mg/kg body weight of an aqueous extract of Cgb for 7 days, 4 mL/kg body weight of LPS for 4 hours, and 1000 mg/kg body weight of an aqueous extract of Cgb for 7 days. At the end of the administration period, the animals were sacrificed, blood was collected via cardiac puncture under light ketamine anaesthesia, and organ samples (brain, liver, heart, kidney, and lungs) were collected. The "Principles of Laboratory Animal Care" (NIH, 1985), were followed in this study, as well

as specific national laws where applicable. The Ad Hoc Animal Ethical Committee of the Department of Biochemistry has reviewed and approved all experiments. In this work, the "Principles of Laboratory Animal Care" (NIH, 1985) and all applicable specific national laws were adhered to. All protocols have been approved by the Ad Hoc Animal Ethical Committee of the Department of Biochemistry.

2.4. Sample preparation

The whole blood samples were centrifuged at 10, 500 × g for 5 min to obtain the plasma, and the erythrocytes were washed with normal saline (three times), centrifuged at 10,500 × g for 5 min, and then both were stored. Thereafter, the animals were quickly dissected; the liver, brain, heart, kidney, and lungs were carefully harvested. 10% homogenization was performed on each organ; briefly, 0.2 g of organ was homogenised in ice-cold homogenization buffer (1.8 mL of 0.05 M phosphate buffer) and centrifuged at 10,500 × g for 5 min, and the supernatant was stored for further assays.

2.5. Biochemical analysis of the oxidative stress marker enzyme activities

The catalase (CAT) and superoxide dismutase (SOD) activities in plasma, erythrocytes (convey oxygen from the lungs), and organs were carried out according to the method of Ogunrinola *et al*. (2016). The modified procedures of Vuori and Kanerva (2018) was used to determine the glutathione-S-transferase activity in the plasma.

2.6. Statistical analysis

The data were expressed as the mean ± S.E.M (standard error of mean) of three replicates in each group. And an analysis of variance (ANOVA) was carried out to test for the level of homogeneity at $P \leq 0.05$ among the groups that are statistically significant using the Statistical Package for Social Sciences version 17.0 (SPSS, Chicago, Illinois).

3. Results and discussion

The lethal dose (LD_{50}) results of the crude aqueous extract of Cgb show that there was no mortality in the rats at various dose levels for 72 hours. This led to the choice of a 1000 mg/kg body weight dose given to the rats.

The effect of an aqueous extract of *Crinum glaucum* bulb (Cgb) on some biomarkers of endotoxin-induced oxidative stress in rats was analysed by assessing the activity of CAT and SOD in the plasma, erythrocytes, brain, liver, lung, heart, and kidney, and GST in the plasma of the control and treated groups. Our team has reported that the aqueous extract of *Crinum glaucum* bulb (Cgb) is not toxic (Ogunrinola *et al.*, 2022b) as observed in our study. Endotoxin (LPS) is a main mediator of sepsis, which includes amplification of the initial inflammatory response followed by immunosuppression and multiple organ dysfunction or failure leading to death (Ma *et al.*, 2020; Fernando *et al.*, 2018), by inducing oxidative stress, which promotes the high production of reactive oxygen species (ROS), including free radicals, hydroxyl radicals, superoxide anion, hydrogen peroxide, and singlet oxygen, as well as nitric oxideand peroxynitrite (Noworyta-Sokołowska *et al.*, 2013; Salehi *et al.*, 2020; Skibska *et al.*, 2022; Zhou *et al.*, 2022; Al-Rikabi *et al.*, 2020; Nandi *et al.*, 2019).

When the release of these free radicals exceeds that of the endogenous antioxidant enzymes (catalase, glutathione-S-transferase (GST), glutathione peroxidase (GPX), and superoxide dismutase (SOD), among others), oxidation of cellular components occurs (Ajuwon *et al.*, 2014; Zhou *et al.*, 2022; Nakai and Tsuruta, 2021; Sharifi-Rad *et al.*, 2020; Kolac *et al.*, 2017). In this study, the injection of LPS into the rats (male and female) resulted in the development of oxidative stress in all compartments by the significant ($P \leq 0.05$) reduction of CAT (Figures 1-4) and SOD (Table 1) activity in the plasma, erythrocytes, brain, liver, lung, heart, and kidney. There is also a significant ($P \leq 0.05$) increased activity of GST (Figure 5) in the plasma compartment. These results are consistent with previous studies demonstrating that LPS induces oxidative stress (Ajuwon *et al.*, 2014; Noworyta-Sokołowska *et al.*, 2013; Zhou *et al.*, 2022; Kolac *et al.*, 2017; Skibska *et al.*, 2022; Sebai *et al.*, 2010). The up- or down-regulation of these enzymes may trigger a negative chain reaction that could lead to cell membrane destruction, the inhibition of major enzymes, the suspension of vital cellular functions, abnormal cell division, the oxidation of deoxyribonucleic acid, and the obstruction of energy production (He *et al.*, 2017; Kurutas, 2015).CAT is primarily found in peroxisomes, a sub-cellular

organelle, but some is also found in the cytoplasm (Fujiki *et al.*, 2020; Hosoi *et al.*, 2017).

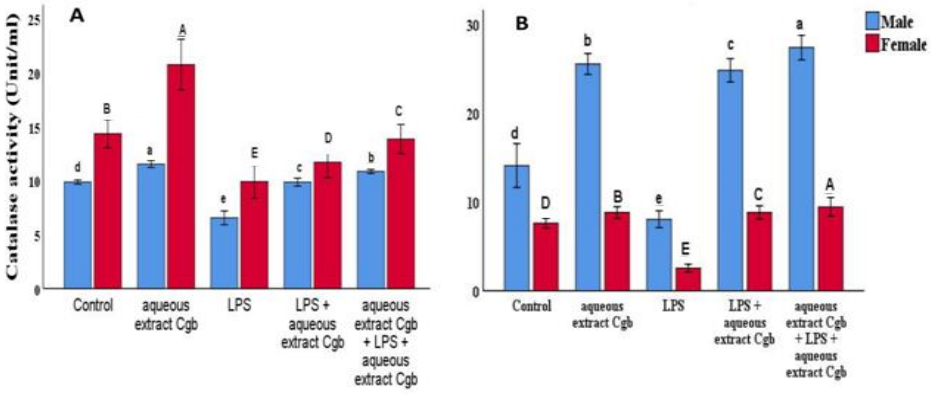

Figure 1. The effect of an aqueous extract of *Crinum glaucum* bulb (Cgb) on plasma (**A**) and erythrocyte (**B**) catalase (CAT) activity in male and female LPS-induced oxidative stress rats. Each bar represents the mean ± standard error of mean (SEM) of 5 rats. Bars with different letters are statistically significant in male and female animals ($P \leq 0.05$). LPS=Lipopolysaccharide.

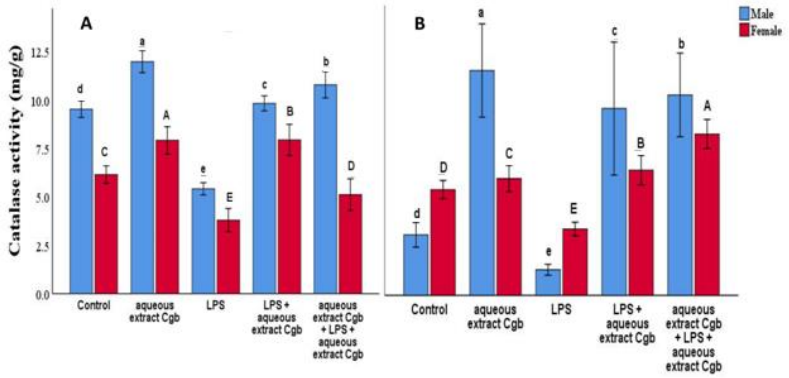

Figure 2. The effect of an aqueous extract of *Crinum glaucum* bulb (Cgb) on brain (**A**) and liver (**B**) catalase (CAT) activity in male and female LPS-induced oxidative stress rats. Each bar represents the mean ± standard error of mean (SEM) of 5 rats. Bars with different letters are statistically significant in male and female animals ($P \leq 0.05$). LPS=Lipopolysaccharide.

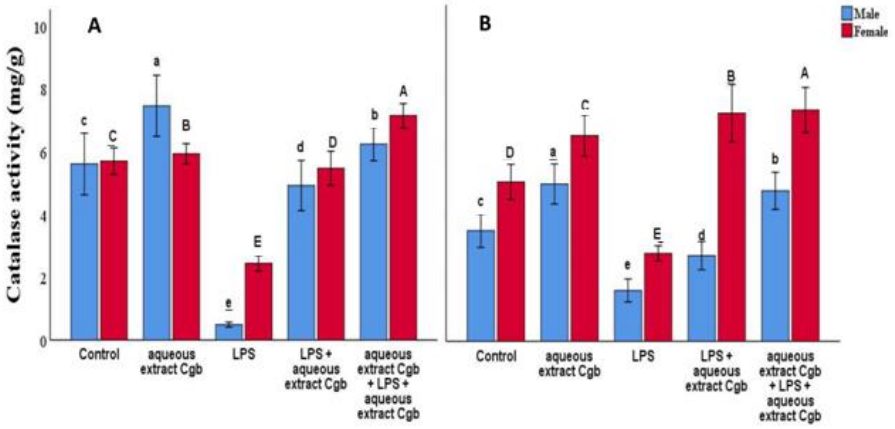

Figure 3. The effect of an aqueous extract of *Crinum glaucum* bulb (Cgb) on lung (**A**) and heart (**B**) catalase (CAT) activity in male and female LPS-induced oxidative stress rats. Each bar represents the mean ± standard error of mean (SEM) of 5 rats. Bars with different letters are statistically significant in male and female animals ($P \leq 0.05$). LPS=Lipopolysaccharide. (*$P \leq 0.05$).

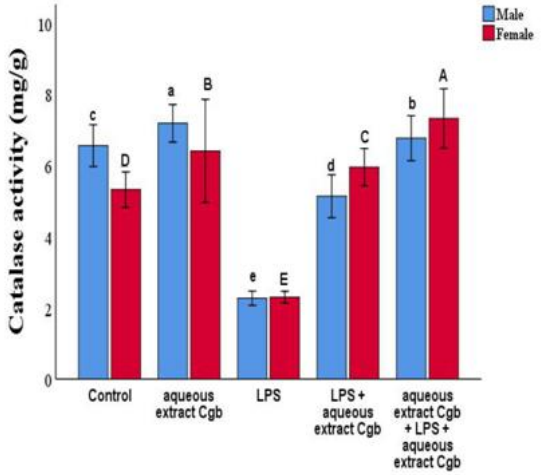

Figure 4. The effect of an aqueous extract of *Crinum glaucum* bulb (Cgb) on kidney catalase (CAT) activity in male and female LPS-induced oxidative stress rats. Each bar represents the mean ± standard error of mean (SEM) of 5 rats. Bars with different letters are statistically significant in male and female animals ($P \leq 0.05$). LPS=Lipopolysaccharide.

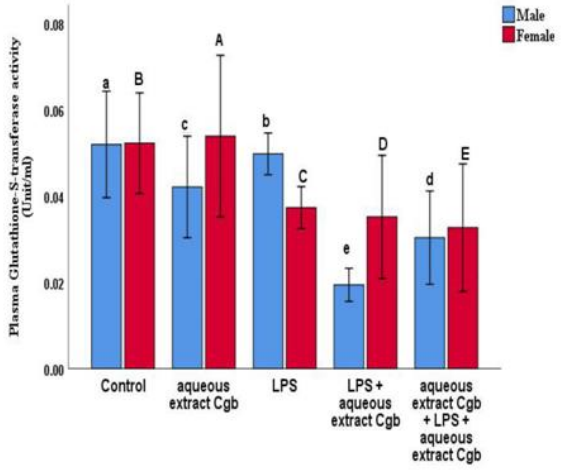

Figure 5. The effect of an aqueous extract of *Crinum glaucum* bulb (Cgb) on plasma glutathione-S-transferase (GST) activity in male and female LPS-induced oxidative stress rats. Each bar represents the mean ± standard error of mean (SEM) of 5 rats. Bars with different letters are statistically significant in male and female animals ($P \leq 0.05$).
LPS=Lipopolysaccharide.

Table 1. The effect of an aqueous extract of *Crinum glaucum* bulb (Cgb) on plasma, erythrocytes, and organ (brain, liver, lung, heart, and kidney) superoxide dismutase (SOD) activity in male and female LPS-induced oxidative stress rats.

Treatment / Parameters		Control (Group 1)	Aqueous extract Cgb (Group 2)	LPS (Group 3)	LPS + Aqueous extractCgb (Group 4)	Aqueous extractCgb + LPS +Aqueous extractCgb (Group 5)
Plasma	M	0.142±0.012^{d}	0.254±0.041^{c}	0.062±0.013^{e}	0.335±0.033^{b}	0.405±0.036^{a}
(Unit/ml)	F	0.676±0.134^{a}	1.106±0.159^{d}	0.229±0.022^{e}	1.145±0.146^{c}	1.279±0.170^{b}
Erythrocytes	M	0.050±0.007^{b}	0.061±0.010^{a}	0.019±0.004^{e}	0.037±0.005^{d}	0.042±0.010^{c}
(Unit/ml)	F	1.962±0.539^{d}	3.053±0.324^{c}	0.753±0.156^{e}	3.595±0.739^{b}	4.433±0.934^{a}
Brain	M	0.079±0.005^{c}	0.089±0.004^{a}	0.042±0.004^{e}	0.073±0.006^{d}	0.085±0.008^{b}
(mg/g tissue)	F	0.032±0.006^{d}	0.051±0.007^{c}	0.011±0.004^{e}	0.056±0.005^{b}	0.062±0.007^{a}
Heart	M	0.131±0.009^{b}	0.153±0.012^{a}	0.060±0.007^{e}	0.085±0.004^{d}	0.099±0.012^{c}
(mg/g tissue)	F	0.041±0.009^{d}	0.063±0.007^{b}	0.022±0.003^{e}	0.048±0.002^{c}	0.179±0.108^{a}
Lung	M	0.436±0.037^{d}	0.629±0.116^{a}	0.049±0.006^{e}	0.493±0.060^{c}	0.585±0.038^{b}
(mg/g tissue)	F	0.038±0.004^{d}	0.052±0.006^{b}	0.026±0.008^{e}	0.043±0.006^{c}	0.059±0.004^{a}
Liver	M	0.463±0.073^{b}	0.549±0.037^{a}	0.037±0.007^{e}	0.287±0.022^{d}	0.333±0.037^{c}
(mg/g tissue)	F	0.058±0.006^{d}	0.061±0.003^{c}	0.023±0.002^{e}	0.065±0.008^{b}	0.074±0.007^{a}
Kidney	M	0.236±0.042^{b}	0.299±0.038^{a}	0.080±0.005^{e}	0.103±0.012^{d}	0.139±0.020^{c}
(mg/g tissue)	F	0.031±0.006^{d}	0.054±0.003^{c}	0.026±0.002^{e}	0.063±0.004^{b}	0.069±0.006^{a}

Values are mean ± SEM for 5 rats in each group; values having different superscripts within a row differ significantly from each other ($P \leq 0.05$). LPS=Lipopolysaccharide. Cgb = *Crinum glaucum* bulb. M=male, F=female.

Additionally, it has been discovered that brassinosteroid-insensitive 1-associated receptor kinase (BAK) localizes in the peroxisomes and regulates CAT export and peroxisome membrane permeability. And that voltage-dependent anion channel 2 (VDAC2) regulates BAK's localization and proapoptotic activity. Catalase is imported into the peroxisome by the peroxisomal targeting signal 1 (PTS1) receptor peroxins 5, which shuttle between the cytoplasm and peroxisomes to import peroxisomal matrix proteins harbouring the PTS1 motif (Fujiki *et al.*, 2020; Apanasets *et al.*, 2014). Hydrogen peroxide molecules,

a primary cause of oxidative stress, are eliminated from the cytoplasm by the CAT that is released from peroxisomes through BAK (Fujiki *et al.*, 2020; Hosoi *et al.*, 2017; Fujiki *et al*., 2017).

In a two-step reaction, CAT reduces two molecules of hydrogen peroxide into one oxygen molecule and two molecules of water (Nandi *et al.*, 2019).The inhibition of cysteine 11 of peroxins 5, which act as redox sensors to reduce the importation of PTS1-containing proteins mediated by BAK, may lead to a decrease in CAT in the cytoplasm due to the intolerable cellular stress caused by the LPS-induced stress group of this study. Therefore, hydrogen peroxide molecules that are to be removed by CAT will accumulate in the cytoplasm (Fujiki *et al.*, 2020; Hosoi *et al.*, 2017; Apanasets *et al.*, 2014; Walton *et al.*, 2017).As observed in this study, the increased concentration of glutathione-S-transferases (GST) activates the conjugation of isothiocyanates with GSH, which is consumed by glutathione peroxidase (GPX) to remove the excess hydrogen peroxide. The increased hydrogen peroxide production, will cause a reduction in the antioxidant enzymes (SOD and CAT).Many illnesses, including diabetes mellitus, vitiligo, cardiovascular diseases, Wilson disease, hypertension, anaemia, some dermatological disorders, Alzheimer's disease, bipolar disorder, and schizophrenia, are linked to decreased or dysfunctional CAT activity (Nandi *et al.*, 2019).

Medicinal plants like Cgb consist of phytochemical constituents exhibiting antioxidant effects that are broadly categorized into the alkaloid, carotenoid, coumarin, flavonoid, phenolic, lignans, stilbenes, tannins, and terpenoid groups, among other organic compounds (Salehi *et al.*, 2020; Myburgh, 2014; Ishola *et al.*, 2013). The flavonoids, which comprise a large group of phenolic compounds, have gained health benefits due to their broad pharmacological activity becausetheir chemical structures are predictive of their antioxidant potential in terms of their radical scavenging, hydrogen- or electron-donation activities (Salehi *et al.*, 2020). The pre- and post-administration of an aqueous extract of Cgb to the LPS-induced oxidative stress rats reverses the action of LPS in all the compartments, as shown in Figures 1-5 and Table 1, respectively, except that the female rats responded more significantly ($P \leq 0.05$) than the male rats.This result corroborated the reports of Ajuwon *et al.* (2014), Kolac *et al*. (2017), Arab *et al*. (2020), Ji *et al*. (2023), Hou *et al*. (2014) and Liu *et al*. (2018).This reversal in the antioxidant enzymes (CAT, SOD, and GST) activities could be due to the high presence of flavonoids in the aqueous extract of Cgb to scavenge the numerous ROS through these mechanisms (Salehi *et al.*, 2020; Hou *et al.*, 2014; Battelli *et al.*, 2016; Battelli *et al.*, 2014): (1) The flavonoids scavenge the free radicals, or ROS, by being able to donate a hydrogen atom to neutralize free radicals, and they may also act by single-electron transfer. The mechanism of action of flavonoids is due to their structural features: (i) an O-dihydroxy (catechol) structure in the B-ring for electron delocalization; (ii) hydroxyl groups at positions 3 on the C-ring and 5 and 7 on the A-ring provide an increase in antioxidant activity; and (iii) a C_2-C_3 double bond combined with the oxo-C_4 on the C-ring. The B-ring hydroxyl structure is the most significant point in scavenging free radicals by stabilizing the hydroxyl, peroxyl, and peroxynitrite radicals through the donation of hydrogen or electrons. (2) Flavonoids inhibit the pro-oxidant enzymes (xanthine oxidoreductase (XOR), lipoxygenase (LOX), and cyclooxygenase (COX)) that are associated with ROS generation. During the metabolism of xanthine to uric acid, the generated molecular oxygen radicalsreact with XOR to release superoxide. The flavonoids' inhibitory activity is due to the planar flavone core (C_2-C_3 double bond), hydroxyl groups at C_5 and C_7, and the carbonyl group at C_4, respectively. Flavonoids inhibit these enzymes with an O-dihydroxy (catechol) moiety in rings A or B, in addition to the C_2-C_3 double bond. And (3) the activation or modulation of antioxidant enzymes (catalase (CAT), superoxide dismutase (SOD), glutathione-S-transferase) by flavonoids interacting with cellular defense systems through the antioxidant-responsive element/electrophile-responsive element (ARE/EpRE) at the hydroxyl group at the 3-position of the C-ring.

Despite the eminent mechanism of flavonoids, polyphenols are well-known as scavengers and chain-breaking phytochemicals. Different mechanisms, such as chemical instability, cellular glutathione (GSH) depletion, and sulfhydryl (SH) interactions, could be responsible for polyphenols' pro-oxidant effects (Salehi *et al.*, 2020). The pro-oxidant activity possessed by the flavonoids and polyphenols present in the aqueous extract of Cgb might be responsible for the up- and

down-regulates the antioxidants (Salehi *et al.*, 2020; Fuentes *et al.*, 2015; Yang *et al.*, 2016).

4. Conclusion

The obtained results indicated that an aqueous extract of Cgb had effective modulatory capacity on the induced-oxidative stress in the female and male animal models. Our findings reveal a new protective mechanism of an aqueous extract of Cgb as a potent antioxidant. The results demonstrated that an aqueous extract of Cgb is an accessible source of natural antioxidants, can be used as a therapeutic agent for oxidative-related diseases, and thus promotes healthy management.

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6. References

Adu, O.B., Adeyemo, G.A., Falua, O.B., Fajana, O.O., Ogunrinola, O.O., Saibu, G.M. and Elemo, B.O. 2021. The effect of *Thaumatococcus danielli* leaf extracts on immunological and oxidative stress markers in rat. *Asian Journal of Biochemistry, Genetics and Molecular Biology*, 7:6-14.

Ajuwon, O.R., Oguntibeju, O.O. and Marnewick, J.L. 2014. Amelioration of lipopolysaccharide-induced liver injury by aqueous rooibos (*Aspalathus linearis*) extract via inhibition of pro-inflammatory cytokines and oxidative stress.*BMC Complementary Alternative Medicine*, 14(1):1-2.

Akintola, A.O., Kehinde, A.O., Adebiyi, O.E. and Ademowo, O.G. 2013. Anti-tuberculosis activities of the crude methanolic extract and purified fractions of the bulb of *Crinum jagus*. *Nigerian Journal Physiological Sciences*, 28(2):135-140.

Alam, M.N., Bristi, N.J. and Rafiquzzaman, M. 2013. Review on in vivo and in vitro methods evaluation of antioxidant activity. *Saudi Pharmaceutical Journal*, 21(2):143-152.

Al-Rikabi, R., Al-Shmgani, H., Dewir, Y.H. and El-Hendawy, S. 2020. In vivo and in vitro evaluation of the protective effects of hesperidin in lipopolysaccharide-induced inflammation and cytotoxicity of cell. *Molecules*, 25(3):478.

Alwaleedi, S.A. 2016. Alterations in antioxidant defense system in hepatic and renal tissues of rats following aspartame intake. *Journal of Applied Biology and Biotechnology*, 4(2): 46-52.

Apanasets, O., Grou, C.P., Van Veldhoven, P.P., Brees, C., Wang, B., Nordgren, M., Dodt, G., Azevedo, J.E. and Fransen, M. 2014. PEX5, the shuttling import receptor for peroxisomal matrix proteins, is a redox-sensitive protein. *Traffic*, 15(1): 94-103.

Arab, Z., Hosseini, M., Mashayekhi, F. and Anaeigoudari, A. 2020. *Zataria multiflora* extract reverses lipopolysaccharide-induced anxiety and depression behaviors in rats. *Avicenna Journal of Phytomedicine*, 10(1): 78-83.

Battelli, M.G., Bolognesi, A. and Polito, L. 2014. Pathophysiology of circulating xanthine oxidoreductase: New emerging roles for a multi-tasking enzyme. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease*, 1842(9): 1502-1517.

Battelli, M.G., Polito, L., Bortolotti, M. and Bolognesi, A. 2016. Xanthine oxidoreductase-derived reactive species: physiological and pathological effects. *Oxidative Medicine and Cellular Longevity*, 2016. Article ID 3527579.

Bertani, B. and Ruiz, N. 2018. Function and biogenesis of lipopolysaccharides. *EcoSal Plus*, 8(1):10-15.

Cahlíková, L., Vaněčková, N., Šafratová, M., Breiterová, K., Blunden, G., Hulcová, D. and Opletal, L. 2019. The genus *Nerine* Herb. (Amaryllidaceae): Ethnobotany, phytochemistry, and biological activity. *Molecules*, 24(23): 4238.

Donald, K.K.B., Irié-N'guessan Amenan Geneviève, E., Etienne, K. and Felix, Y.H. 2018. Evaluation of anti-inflammatory activity of *Crinum scillifolium* extracts in Wistar rats. *Cardiovascular diseases*, 6(4): 77-82.

Erhirhie, E.O., Ihekwereme, C.P. and Ilodigwe, E.E. 2018. Advances in acute toxicity testing: strengths, weaknesses and regulatory acceptance. *Interdisciplinary toxicology*, 11(1): 5-12.

Fernando, S.M., Rochwerg, B. and Seely, A.J. 2018. Clinical implications of the third international

consensus definitions for sepsis and septic shock (Sepsis-3). *Cmaj*, 190(36): E1058-E1059.

Fuentes, F., Paredes-Gonzalez, X. and Kong, A.N.T. 2015. Dietary glucosinolates sulforaphane, phenethyl isothiocyanate, indole-3-carbinol/3, 3′-diindolylmethane: Antioxidative stress/inflammation, Nrf2, epigenetics/epigenomics and in vivo cancer chemopreventive efficacy. *Current Pharmacology Reports*, 1: 179-196.

Fujiki, Y., Abe, Y., Imoto, Y., Tanaka, A.J., Okumoto, K., Honsho, M., Tamura, S., Miyata, N., Yamashita, T., Chung, W.K. and Kuroiwa, T. 2020. Recent insights into peroxisome biogenesis and associated diseases. *Journal of Cell Science*, 133(9): jcs236943.

Fujiki, Y., Miyata, N., Mukai, S., Okumoto, K. and Cheng, E.H. 2017. BAK regulates catalase release from peroxisomes. *Molecular & Cellular Oncology*, 4(3): e1306610.

Guide for the care and use of laboratory animals. NIH Publication. 1985;85–23. Revised.1985.

Halawa, A.A., El-Adl, M.A., Hamed, M.F., Balboula, A.Z. and Elmetwally, M.A. 2018. Lipopolysaccharide prompts oxidative stress and apoptosis in rats' testicular tissue. *Journal of Veterinary. Health*, 1: 20-31.

He, L., He, T., Farrar, S., Ji, L., Liu, T. and Ma, X. 2017. Antioxidants maintain cellular redox homeostasis by elimination of reactive oxygen species. *Cellular Physiology and Biochemistry*, 44(2): 532-553.

Hosoi, K.I., Miyata, N., Mukai, S., Furuki, S., Okumoto, K., Cheng, E.H. and Fujiki, Y. 2017. The VDAC2–BAK axis regulates peroxisomal membrane permeability. *Journal of Cell Biology*, 216(3): 709-722.

Hou, X., Zhang, J., Ahmad, H., Zhang, H., Xu, Z. and Wang, T. 2014. Evaluation of antioxidant activities of ampelopsin and its protective effect in lipopolysaccharide-induced oxidative stress piglets. *PloS one*, 9(9): e108314.

Houghton, P.J., Agbedahunsi, J.M. and Adegbulugbe, A. 2004. Choline esterase inhibitory properties of alkaloids from two Nigerian *Crinum* species. *Phytochemistry*, 65(21): 2893-2896.

Ishola, I.O., Olayemi, S.O. and Idowu, A.R. 2013. Anticonvulsant, anxiolytic and hypnotic effects of aqueous bulb extract of *Crinum glaucum* A. chev (Amaryllidaceae): Role of GABAergic and nitrergic systems. *Pakistan Journal of Biological Sciences*: PJBS, 16(15): 701-710.

Ji, M., Deng, Z., Rong, X., Li, R., You, Z., Guo, X., Cai, C., Zhao, Y., Gao, P., Cao, G. and Li, B. 2023. *Naringenin* Prevents Oxidative Stress and Inflammation in LPS-Induced Liver Injury through the Regulation of LncRNA-mRNA in Male Mice. *Molecules*, 28(1): 198-103.

Kolac, U.K., Ustuner, M.C., Tekin, N., Ustuner, D., Colak, E. and Entok, E. 2017. The anti-inflammatory and antioxidant effects of *Salvia officinalis* on lipopolysaccharide-induced inflammation in rats. *Journal of Medicinal Food*, 20(12): 1193-1200.

Kurutas, E.B. 2015. The importance of antioxidants which play the role in cellular response against oxidative/nitrosative stress: current state. *Nutrition Journal*, 15(1): 1-22.

Liu, Y., Li, Z., Xue, X., Wang, Y., Zhang, Y. and Wang, J. 2018. Apigenin reverses lung injury and immunotoxicity in paraquat-treated mice. *International Immunopharmacology*, 65: 531-538.

Ma, J., Xu, X., Wang, R., Yan, H., Yao, H., Zhang, H., Jiang, S. and Xu, A. 2020. Lipopolysaccharide exposure induces oxidative damage in *Caenorhabditis elegans*: Protective effects of carnosine. *BMC Pharmacology and Toxicology*, 21(1): 1-9.

Mohammad, S. and Thiemermann, C. 2021. Role of metabolic endotoxemia in systemic inflammation and potential interventions. *Frontiers in immunology*, 11: 594150.

Myburgh, K.H. 2014. Polyphenol supplementation: Benefits for exercise performance or oxidative stress? *Sports Medicine*, 44: 57-70.

Nakai, K. and Tsuruta, D. 2021. What are reactive oxygen species, free radicals, and oxidative stress in skin diseases? *International Journal of Molecular Sciences*, 22(19): 10799.

Nandi, A., Yan, L.J., Jana, C.K. and Das, N. 2019. Role of catalase in oxidative stress-and age-associated degenerative diseases. *Oxidative Medicine and Cellular Longevity*, 11: 2019.

Noworyta-Sokołowska, K., Górska, A. and Gołembiowska, K. 2013. LPS-induced oxidative stress and inflammatory reaction in the rat striatum. *Pharmacological Reports*, 65(4): 863-869.

Ogunrinola, O.O., Kanmodi, R.I., Adeyemo, G.A., Ogunrinola, O.A., Olatunji, K.O., Fayemi, A.O., Sunday, A.J., Adu, O.B. and Elemo, B.O. 2022a.

Crinum glaucum Bulb Extract Improves the Lipid Profile of Endotoxin-Induced Wistar Rats. *Asian Journal of Research in Biochemistry*, 11(2): 10-17.

Ogunrinola, O.O., Kanmodi, R.I., Ogunrinola, O.A., Adegbulugbe, J.A., Adu, O.B. 2022b. Cholesterol and triglycerides concentrations of lipopolysaccharide-induced inflammatory male rat in response to *Petiveria alliacea* L. Leaf Extract. *Journal of Applied Sciences*, 22(2):100-106.

Ogunrinola, O.O., Wusu, D.A., Fajana, O.O., Olaitan, S.N., Smith, Z.O. and Bolaji, A.R.I. 2016. Effect of low level cadmium exposure on superoxide dismutase activity in rat. *Tropical Journal of Pharmaceutical Research*, 15(1): 115-119.

Olatunji K.O., Ogunrinola O.A., Ogunrinola O.O., Igbalaye O.J., Adeniyi A.E., Ahmad A.A., Aribisala B.S., Elemo B.O. 2023. Therapeutic Role of *Crinum glaucum* Bulb against Haematological and Hepatic Enzyme Alterations in a Rat Model. *Asian Journal of Biochemistry, Genetics and Molecular Biology*, 14(2):12-22.

Pizzino, G., Irrera, N., Cucinotta, M., Pallio, G., Mannino, F., Arcoraci, V., Squadrito, F., Altavilla, D. and Bitto, A. 2017. Oxidative stress: harms and benefits for human health. *Oxidative Medicine and Cellular Longevity*, 2017: Article ID 8416763.

Rahal, A., Kumar, A., Singh, V., Yadav, B., Tiwari, R., Chakraborty, S. and Dhama, K. 2014. Oxidative stress, prooxidants, and antioxidants: The interplay. *BioMed Research International*, 2014. Article ID 761264.

Refaat, J., Kamel, M.S., Ramadan, M.A. and Ali, A.A. 2013. *Crinu*m; an endless source of bioactive principles: A review. Part V. Biological profile. *International Journal of Pharmaceutical Sciences and Research*, 4(4): 1239.

Salehi, B., Azzini, E., Zucca, P., Maria Varoni, E., V. Anil Kumar, N., Dini, L., Panzarini, E., Rajkovic, J., Valere Tsouh Fokou, P., Peluso, I. and Prakash Mishra, A. 2020. Plant-derived bioactives and oxidative stress-related disorders: A key trend towards healthy aging and longevity promotion. *Applied Sciences*, 10(3): 947-951.

Sebai, H., Sani, M., Yacoubi, M.T., Aouani, E., Ghanem-Boughanmi, N. and Ben-Attia, M. 2010. Resveratrol, a red wine polyphenol, attenuates lipopolysaccharide-induced oxidative stress in rat liver. *Ecotoxicology and Environmental Safety*, 73(5): 1078-1083.

Sharifi-Rad, M., Anil Kumar, N.V., Zucca, P., Varoni, E.M., Dini, L., Panzarini, E., Rajkovic, J., Tsouh Fokou, P.V., Azzini, E., Peluso, I. and Prakash Mishra, A. 2020. Lifestyle, oxidative stress, and antioxidants: Back and forth in the pathophysiology of chronic diseases. *Frontiers in Physiology*, 11: 694-698.

Sies, H. 2015. Oxidative stress: a concept in redox biology and medicine. *Redox Biology*, 4: 180-183.

Skibska, B., Goraca, A., Skibska, A. and Stanczak, A. 2022. Effect of alpha-lipoic acid on rat ventricles and atria under LPS-induced oxidative stress. *Antioxidants*, 11(4): 734.

Stefanov, G., Briyal, S., Pais, G., Puppala, B. and Gulati, A. 2020. Relationship between oxidative stress markers and endothelin-1 levels in newborns of different gestational ages. *Frontiers in Pediatrics*, 8: 279.

Stepanić, V., Trošelj, K.G., Lučić, B., Marković, Z. and Amić, D. 2013. Bond dissociation free energy as a general parameter for flavonoid radical scavenging activity. *Food Chemistry*, 141(2): 1562-1570.

Tian, H., Liu, Q.J., Wang, J.T. and Zhang, L. 2021. Antimicrobial crinane-type alkaloids from the bulbs of *Crinum latifolium*. *Journal of Asian Natural Products Research*, 23(11): 1023-1029.

Umar, H.I., Saliu, T.P., Josiah, S.S., Ajayi, A. and Danjuma, J.B. 2021. In silico studies of bioactive compounds from selected African plants with inhibitory activity against nitric oxide synthase and arginase implicated in asthma. *Egyptian Journal of Medical Human Genetics*, 22: 1-16.

Vuori, K.A. and Kanerva, M. 2018. Glutathione-S-Transferase (GST) activity assay for copepod samples. *Journal of Biological Chemistry*, 249: 7130-7139.

Walton, P.A., Brees, C., Lismont, C., Apanasets, O. and Fransen, M. 2017. The peroxisomal import receptor PEX5 functions as a stress sensor, retaining catalase in the cytosol in times of oxidative stress. *Biochimica Et Biophysica Acta (BBA)-Molecular Cell Research*, 1864(10): 1833-1843.

Xu, T., Liu, R., Zhu, H., Zhou, Y., Pei, T. and Yang, Z. 2022. The inhibition of LPS-induced oxidative stress and inflammatory responses is associated with the protective effect of (-)-Epigallocatechin-3-Gallate on bovine hepatocytes and murine liver. *Antioxidants*, 11(5): 914.

Yang, L., Palliyaguru, D.L. and Kensler, T.W. 2016. Frugal chemoprevention: targeting Nrf2 with foods rich in sulforaphane. *In Seminars in oncology*, 43(1): 146-153.

Zhou, Y., Hu, X., Zhong, S., Yu, W., Wang, J., Zhu, W., Yang, T., Zhao, G., Jiang, Y. and Li, Y. 2022. Effects of continuous LPS induction on oxidative stress and liver injury in weaned piglets. *Veterinary Sciences*, 10(1): 22-26.