

Effects Of *Gongronema Latifolium* (Benth.) Leaf Extract on Cardiac Glutathione and Dopamine Antioxidant Systems

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Research Article

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Abstract

This study investigates the effects of *Gongronema latifolium* methanolic leaf extract (GLL) on antioxidant enzyme activities and dopamine levels in cardiac tissue. Female Wistar rats (150 ± 30 g) were divided into four groups, one control group and three treatment groups (treated with GLL at doses of 250, 500, and 1000 mg/kg for 28 days). The animals were sacrificed after 28 days and the hearts were excised for biochemical analysis (reduced glutathione (GSH) level, glutathione peroxidase (GPx) activity, glutathione S-transferase (GST) activity, superoxide dismutase (SOD) activity, and dopamine level). Results showed dose-dependent modulation of these parameters. GSH and dopamine levels significantly increased at higher doses, enhancing antioxidative defences and potentially supporting cardiovascular function. GPx activity showed sustained elevation across doses, while SOD activity showed a pronounced dose-independent increase, highlighting robust antioxidant effects. GST activity, however, peaked at moderate doses (250 mg/kg), suggesting a biphasic response. These findings show the potential of GLL as a cardioprotective agent. This study contributes to the understanding of its role in mitigating oxidative stress and improving cardiovascular health. Higher doses could overwhelm detoxification pathways, showcasing the need for well-optimized dosages. Future research should explore the molecular pathways underlying these effects and assess GLL's therapeutic potential against cardiovascular disorders.

INTRODUCTION

The use of medicinal plants in developing nations is a major fabric of both traditions and culture, with these traditions being intergenerational (Nwangwu *et al.*, 2009). Medicinal plants are composed of diverse kinds of compounds with medicinal properties, making them important candidates for the development of new antibacterial and antioxidant medications (Sibanda *et al.*, 2007). *G. latifolium* has been especially singled out for its rich phytochemical compositions which confer on it its antioxidant, anti-inflammatory, and cardio-protective properties (Ezejiofor *et al.*, 2020). *G. latifolium* is an edible rainforest plant of West African Origin (Nelson, 1965). It is indigenous to both the South-Eastern as well as South-Western parts of Nigeria (Owu *et al.*, 2012). It is widely dispersed in the African forest and family farms as wild, semi-wild and cultivated (Okafor, 1980). It can be propagated by seed or stem (Softwood, semi-hardwood and hardwood) cuttings (Agbo and Obi, 2006). Known locally as 'Utazi' or 'Arokeke,' it serves as a remedy for ailments like diabetes, hypertension, and malaria, among others. It is highly valued for its medicinal and nutritional contributions, often used as both a spice and a vegetable in Western African cuisine and has been historically employed to regulate weight in lactating women and enhance female fertility. Earlier studies have highlighted its potential hypoglycemic and antihyperglycemic properties (Ugochukwu and Babady, 2002), further placing emphasis on its medicinal importance. *G. latifolium* extracts have shown radioprotective effects, reducing oxidative stress in irradiated rats, and suggesting potential prophylactic applications (Okeke *et al.*, 2022).

Knowledge can be inferred from existing literature about the biochemical mechanism through which it promotes cardiac antioxidant systems. A key mechanism is through the modulation of oxidative stress

and inflammatory biomarkers. Studies have illustrated that phytochemical constituent in the plant (flavonoids, saponins, and alkaloids) are useful in restoring antioxidant enzyme activity in cardiac tissues under pathological conditions. In models of myocardial injury and diabetic cardiomyopathy, administration of *G. latifolium* extracts significantly increased the activity of several important antioxidant enzymes including superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione S-transferase (GST), while reducing malondialdehyde (MDA), a marker of lipid peroxidation (Okesola et al., 2020; Imo, 2017). These effects are likely mediated by the plant's ability to rummage reactive oxygen species (ROS), chelate transition metals, and upregulate endogenous antioxidant systems. *G. latifolium* has also been shown to suppress inflammation-related cardiac injury by reducing levels of tumor necrosis factor-alpha (TNF- α) and C-reactive protein, (Okon et al., 2022). These findings suggest that the cardioprotective antioxidant mechanism of *G. latifolium* is based on its ability to temper redox balance and inflammatory pathways.

The main aim of this study is to provide preliminary evidence supporting the use of extracts of *G. latifolium* as potential cardio-protective agents and lays a foundation for future molecular studies. This study, therefore, outlines the effects of *G. latifolium* on key antioxidant systems, such as SOD, GPx, and GST, suggesting that *G. latifolium* enhances the heart's antioxidant defence mechanisms. The study also evaluated the potential of *G. latifolium* to modulate cardiac dopamine levels, linking it to oxidative stress response and cardiovascular function. While the antioxidant benefits of *G. latifolium* are well-supported, the literature does not extensively address the potential side effects of overconsumption. This gap suggests a need for further research to explore any adverse effects associated with high intake levels, ensuring safe consumption practices.

MATERIALS AND METHODS

Chemicals and Reagents

Thiobarbituric acid, trichloroacetic acid, reduced glutathione, 5,5'-Dithiobis(2-nitrobenzoic acid) (DTNB/Ellman's reagent), epinephrine, ferric cyanide, Folin-Ciocalteu's reagent, and 1,2-dichloro-4-nitrobenzene (CDNB), Reagents were sourced from British Drug House and Sigma-Aldrich. Methanol was supplied by Scharlau (Spain), and all other chemicals were of analytical grade.

Plant Collection and Extract Preparation

Fresh *G. latifolium* leaves were bought from a local market in Ife, air-dried, pulverized, and sequentially macerated in diethyl ether and 80% methanol. The methanolic extract was obtained by evaporation, dried, and stored in a desiccator until use.

Animal Handling and Experimental Design

Female Wistar rats (150 ± 30 g) were used. The animals were kept under standard environmental conditions in the animal facility of the Department of Chemical Sciences, Kings University, Odeomu, Nigeria. They were fed with standard rat chow (Vital Feeds, Lagos, Nigeria) and water, *ad libitum*. Animal handling and use also conformed to the standard guidelines of the Committee on Care and Use of Experimental Animal Resources published by the National Institutes of Health, in 1985. Age-matched animals were divided into four groups ($n = 5$ per group) and were treated as follows: one control group received vehicle (1% DMSO and distilled water), and three treatment groups received *G. latifolium* at doses of 250, 500, and 1000 mg/kg respectively. Treatments were administered orally for 28 days, after which animals were sacrificed, and their hearts excised for biochemical analyses.

Tissue Processing for Biochemical Estimations

Heart tissues (10% w/v) were homogenized in 0.1M phosphate-buffered saline (PBS, pH 7.4), using a Teflon homogenizer and the mixture was centrifuged at $10,000 \times g$ at 4°C for 15 minutes. The supernatants obtained were used for biochemical estimations.

Assay for Reduced Glutathione (GSH) Level

GSH concentration in tissue homogenates was estimated as previously reported (Beutler *et al.*, 1963; Sunil *et al.*, 2011). Tissue homogenates (0.2 ml) were added to a mixture having 1.8 ml of distilled water and 3 ml of 4% Sulfosalicylic acid (SSA) and centrifuged at $1500 \times g$ for 5 min. The supernatant (1 ml) was mixed with 4 ml of 0.1 M phosphate buffer (pH 7.4) and then reacted with 0.5 ml of 5,5-dithio-bis-(2-nitrobenzoic acid (DTNB). The yellow chromophore produced was read at 412 nm against a reagent blank. The glutathione concentration in the homogenate was estimated by extrapolation from a standard glutathione curve.

Assay for Determination of Glutathione peroxidase (GPx) activity

Glutathione peroxidase activity was determined according to the method of Haque *et al.*, (2003). The reaction mixture contained 500 μl of 0.1M phosphate buffer pH 7.4 100 μl of 10mM Sodium azide, 200 μl of 4mM GSH, 100 μl of 2.5mM H_2O_2 were added to 500 μl of the heart homogenate sample, after which 600 μl of distilled water were added and mixed thoroughly. The reaction mixture was incubated at 37°C for 3 mins after which 0.5 ml 10% trichloroacetic acid (TCA) was added and thereafter centrifuged at 3000 rpm for 5 mins. To 1 ml of each of the supernatants, 2 ml of K_2HPO_4 and 1 ml of 0.04% DTNB were added, and the absorbance was read at 412 nm against a blank.

Assay for Glutathione Transferase Activity

Glutathione transferase (GST) activity was determined according to the method of Habig *et al.* (1974). The reaction medium consisted of 30 µl reduced glutathione (0.1 M), 150 µl CDNB (20 mM), 2.79 ml phosphate buffer (0.1 M, pH 6.5) and 30 µl supernatant in a cuvette inside the spectrophotometer. The blank cuvette, on the other hand, did not have supernatant but instead 2.82 ml of buffer. The reaction was allowed to run for 3 min and the absorbance was taken every 60 s each time against the blank at 340 nm. The temperature was kept at approximately 31°C throughout the experiment. GST activity was calculated using the molar extinction coefficient of CDNB ($9.6 \text{ mm}^{-1} \text{ cm}^{-1}$)

Assay for Superoxide Dismutase Activity

Superoxide dismutase activity (SOD) was evaluated according to the method of Kakkar and others (Kakkar *et al.*, 1984). Tissue homogenates (1 ml) were mixed with 2.5 ml of 0.05 M carbonate buffer (pH 10.2) and equilibrated in a spectrophotometer before the addition of 0.3 ml of freshly prepared 0.3 mmol epinephrine to start the reaction. The absorbance was read at 480 nm every 30 s for 150 s. The blank solution contained PBS instead of homogenates. The change in absorbance per minute of the test sample was divided by the change in absorbance per minute of the blank to obtain percentage inhibition. The amount of protein required for 50% inhibition of the oxidation of adrenaline to adrenochrome was estimated as one unit of SOD activity in the tissue.

Evaluation of Dopamine Levels

The level of dopamine was measured by the method of Guo *et al.*, (2009). Homogenate (0.1 ml) was incubated with a mixture having potassium ferricyanide (5 mM, 0.1 ml), FeCl_3 (5 mM, 0.1 ml) and NaH_2PO_4 (pH 4.0, 2.5 ml) in room temperature for 35 min. The absorbance was taken at 735 nm against a reagent blank and dopamine level was estimated from the dopamine hydrochloride standard curve.

Determination of Total Protein Content

Total protein content was estimated by the method of Lowry and others (1951). Tissue homogenate (0.2 ml) was mixed with freshly prepared Reagent C (1 ml) which is made up of Reagent A (2% Sodium Carbonate and 0.1N Sodium hydroxide) and Reagent B (0.5% Copper Sulphate and 1% Potassium tartrate) and allowed to stand for 10 min at room temperature. Then 0.1 ml of Reagent D which is a mixture of Folin Ciocalteu reagent and distilled water (1:2) was added and the absorbance was read at 750 nm after 30 min. The total protein content was estimated from a bovine serum albumin standard curve.

Statistical Analysis

All data derived from the animal experiment analysis was expressed as group mean $\pm$ standard deviation. The experimental results were analysed using the one-way analysis of variance (ANOVA) followed by Tukey multiple comparison tests. In all the tests, $P < 0.05$ was taken as statistical

significance. The statistical significance software used to analyse the data was GraphPad Prism 6.01 (GraphPad Software Inc., CA, USA).

RESULTS

Effect of *Gongronema latifolium* Methanolic Leaf Extract on Cardiac Reduced Glutathione Levels

The effect of *G. latifolium* leaf methanolic extract (GLL) on reduced glutathione (GSH) levels in the hearts of rats is shown in Fig. 1. There was a significant decrease in the GSH level in the heart of rats administered 500 ($P = 0.0011$) and 1000 ($P < 0.0001$) mg/kg GLL in a dose-dependent manner compared to the control. The cardiac GSH level in rats treated with 250 mg/kg GLL were not significantly ($P = 0.1020$) different from the control.

Effects of *Gongronema Latifolium* Methanolic Leaf Extract on Cardiac Glutathione Peroxidase Activity

Figure 2 shows the effect of GLL on glutathione peroxidase (GPx) activity in the heart of rats. The activity of GPx decreased significantly ($P < 0.0001$) in the hearts of rats administered 500 and 1000 mg/kg GLL compared to the control. The GPx activity in the heart of rats administered 250 mg/kg GLL was not significantly ($P = 0.0813$) different from control.

Effect of *Gongronema Latifolium* Methanolic Leaf Extract on Cardiac Glutathione S-Transferase Activity

The effect of GLL on glutathione S-transferase (GST) activity in the hearts of rats is shown in Fig. 3. The GST activity in the hearts of rats administered 250 mg/kg GLL increased significantly ($P = 0.0343$) compared to control. Cardiac GST activity of rats administered 500 mg/kg ($P = 0.0548$) and 1000 mg/kg ($P = 0.9388$) GLL were not significantly different from control. The results also show a biphasic response in glutathione S-transferase (GST) activity, which peaked at moderate doses (250 mg/kg), highlighting the importance of dosage optimization for effective detoxification.

Effect of *Gongronema latifolium* Methanolic Leaf Extract on Cardiac Superoxide Dismutase Activity

Figure 4 shows the effect of GLL on superoxide dismutase activity in the hearts of rats. The activity of superoxide dismutase (SOD) the heart of rats administered 500 mg/kg decreased significantly ($P < 0.0001$) but increased significantly ($P < 0.0001$) in rats administered 1000 mg/kg GLL compared to control. The SOD activity in the heart of rats administered 250 mg/kg GLL was not significantly ($P = 0.7054$) different from control. Superoxide dismutase (SOD) activity showed a pronounced, dose-independent alteration.

Effects of *Gongronema latifolium* Methanolic Leaf Extract on Cardiac Dopamine Levels

The effect of GLL on dopamine levels in the hearts of rats is shown in Fig. 5. Dopamine levels decreased significantly ($P = 0.0044$) in the hearts of rats administered 250 mg/kg GLL, did not change significantly

($P = 0.9977$) in rat treated with 500 mg/kg but increased significantly ($P = 0.0063$) in 1000 mg/kg GLL compared to control.

The results indicate that GLL modulates key antioxidant enzymes and dopamine levels, enhancing cardiac defences against oxidative stress.

DISCUSSION

Gongronema latifolium methanolic leaf extract is widely recognized for its antioxidant properties, which are generally considered beneficial. The plant's extracts have been previously reported to show significant antioxidant activities, including the ability to reduce lipid peroxidation and scavenge free radicals (Okoko *et al.*, 2021). These effects are attributed to the presence of various phytochemicals and essential oils (Chinwe and Usunomena, 2017; Eze, 2018). *G. latifolium* extracts have also shown radioprotective effects, reducing oxidative stress in irradiated rats, and suggesting potential prophylactic applications (Okeke *et al.*, 2022). The plant's abundance of phytochemicals, including phenolic compounds, alkaloids, saponins, and flavonoids, has been reported to be responsible for its health advantages (Olugbodi *et al.*, 2019). Though the antioxidant benefits are well-documented, caution about overconsumption is not extensively discussed in existing literature. In this study, the effects of Methanolic Leaf extract of *G. latifolium* on Cardiac glutathione and dopaminergic antioxidant systems are shown to be dosage dependent. This supports earlier reports that methanol extracts of *G. latifolium* potentiated a concentration-dependent increase in antioxidant activity, comparable to standard drugs used for such purposes (Chidi *et al.*, 2017). This shows that though traditional herbal administrations of the leaves of *G. latifolium* have been without caution towards the side effects of overconsumption, the effects of *G. latifolium* extracts on antioxidant systems are overall generally positive.

Reduced glutathione (GSH) concentrations are decreased in a dosage-dependent manner. This indicates that the extracts of *G. latifolium* may act by directly increasing the mechanisms of synthesis of antioxidant enzymes and molecules. Similarly, glutathione peroxidase (GPx) activity decreased at higher doses of *G. latifolium*, showing a potential improving impact on the heart's ability to detoxify peroxides. Lower dosages of *G. latifolium* extracts seem to improve GST activity but at higher dosages, activity is less pronounced showing a biphasic response, with moderate doses enhancing detoxification pathways and higher doses overwhelming the system. *G. latifolium* extracts dose-independent alteration on cardiac SOD activity. This result supports earlier studies on the function of SOD in attenuating oxidative damage in cardiovascular tissues (Griendling & FitzGerald, 2003). In addition, higher doses of extracts of *G. latifolium* resulted in significant increases in cardiac dopamine (DA) levels, showing a potential adaptive response to oxidative stress with elevated dopamine potentially helping to mitigate damage and support cardiac function. *G. latifolium* extract has been previously reported to increase the activities of antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and glutathione transferase (GST) in numerous studies. This enhancement in enzyme activity helps in reducing oxidative stress markers in cardiac tissues (Okesola *et al.*, 2020; Okon *et al.*, 2022). The medication of *G. latifolium* extract has been shown to regulate neurotransmitter levels (including

dopamine), in diabetic rats, which is crucial for supporting cardiac function and reducing oxidative stress (Ojo *et al.*, 2020). The observed modulation of GSH, GPx, GST, and SOD activities, accompanied by changes in cardiac dopamine levels, suggests that *G. latifolium* extracts can improve the heart's antioxidant defences and protect against oxidative stress-induced damage.

These results are a foundation of proof of *G. latifolium* as a potential cardio-protective agent, though further studies are needed to clarify molecular mechanisms and find the best therapeutic doses. The findings thus provide insights into the cardio-protective mechanisms of GLL. The plant's ability to influence and modulate key antioxidant systems and its impact on cardiac dopamine levels, expose its multi-pronged cardioprotective mechanisms. This study has offered significant insights into the effects of *G. latifolium* on cardiac antioxidant systems and its potential medico-therapeutic implications for cardiovascular health. While the methanolic leaf extract of *G. latifolium* shows promise in modulating cardiac glutathione and dopamine antioxidant systems, it is important to put into consideration the potential for variability in individual responses to different dosages. For example, 250 mg/kg of GLL did not significantly alter cardiac GSH level, GPx and SOD activity; 500 and 1000 mg/kg of GLL did not significantly change cardiac GST activity; and 500 mg/kg GLL did not significantly alter cardiac dopamine levels in rats compared to control in rats.

Further research is needed to prove standardized dosing regimens and to explore the long-term effects of the extract on cardiac and dopaminergic health. Future studies should focus on finding and characterizing the specific molecular pathways by which *G. latifolium* affects cardiac antioxidant systems. This could involve further research into the plant's impact on gene expression with oxidative stress and antioxidant defence mechanisms. Adequate research into the dosage response relationship of *G. latifolium* to decide the best dosage for therapeutic effects is also necessary. Studies should include a wider range of dosages and possibly different forms of extracts to ascertain the most effective and safe concentrations for clinical use.

Declarations

All procedures involving animal handling and care were conducted in accordance with international guidelines for the use and care of laboratory animals. Ethical approval for the study was granted by the Health Research Ethics Committee of the Institute of Public Health, Obafemi Awolowo University, Ile-Ife, Nigeria.

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Declaration of Interest: The authors report there is no conflict of interest to declare.

Data Availability: Enquiries about data availability should be directed to the first author and corresponding author.

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Figures

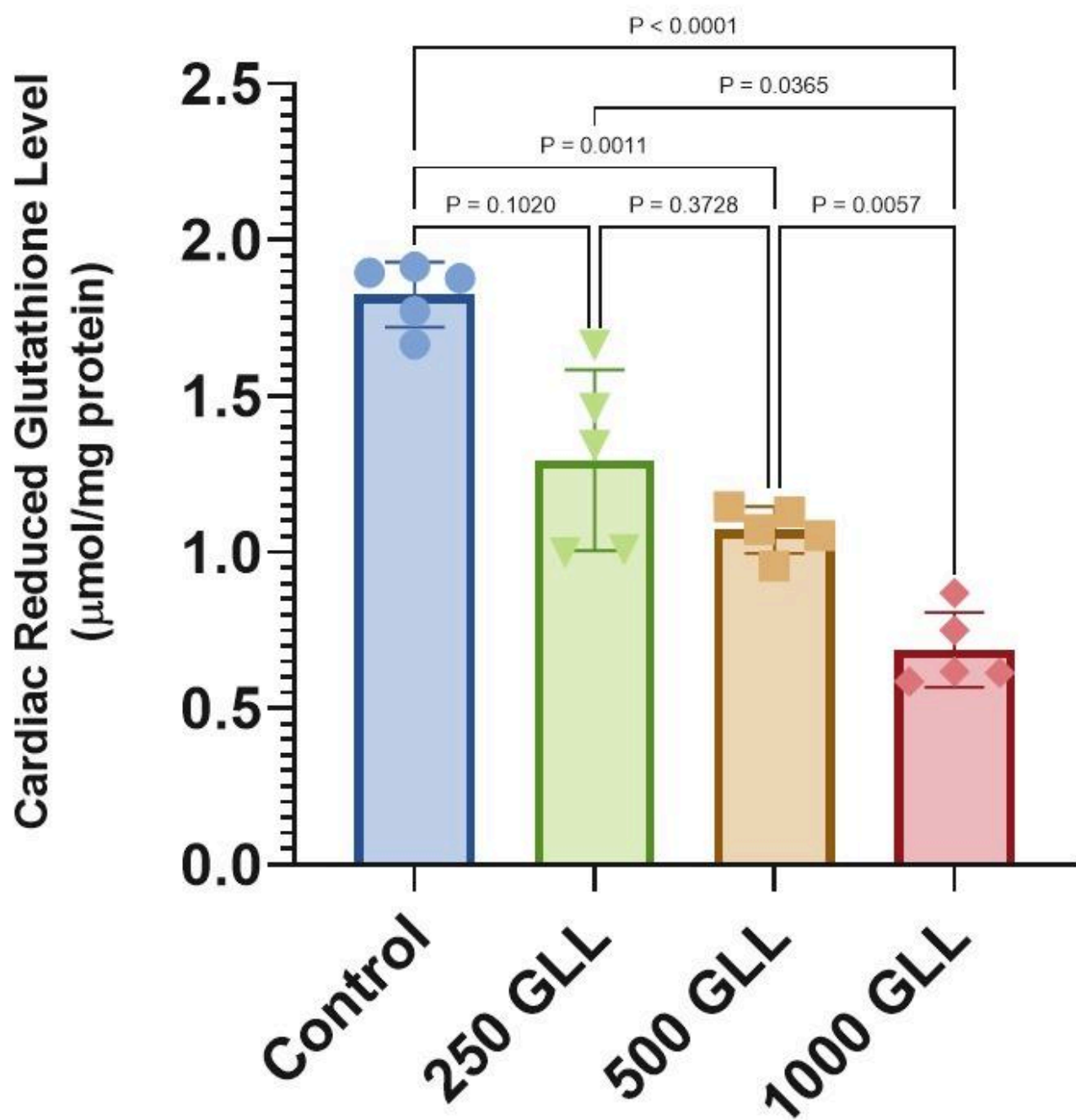


Figure 1

Effect of *Gongronema Latifolium* Methanolic Leaf Extract on Cardiac Reduced Glutathione Levels; Results are expressed as mean $\pm$ SD (n = 5) and analysed using a one-way ANOVA and Tukey's multiple comparisons test. GLL: *Gongronema Latifolium* Methanolic Leaf Extract.

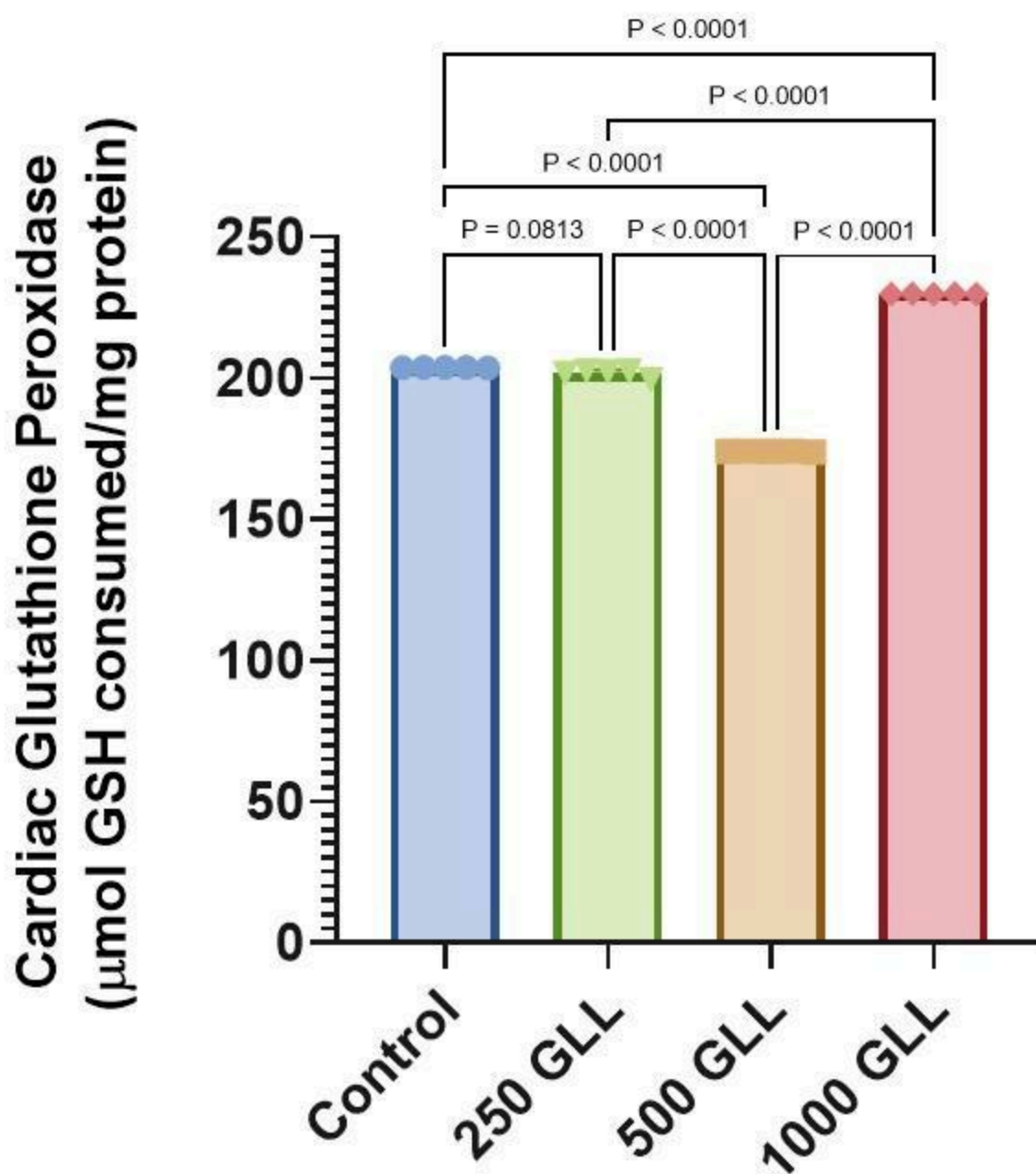


Figure 2

Effect of *Gongronema Latifolium* Methanolic Leaf Extract on Cardiac Glutathione Peroxidase Activity; Results are expressed as mean $\pm$ SD ($n = 5$) and analysed using a one-way ANOVA and Tukey's multiple comparisons test. GLL: *Gongronema Latifolium* Methanolic Leaf Extract.

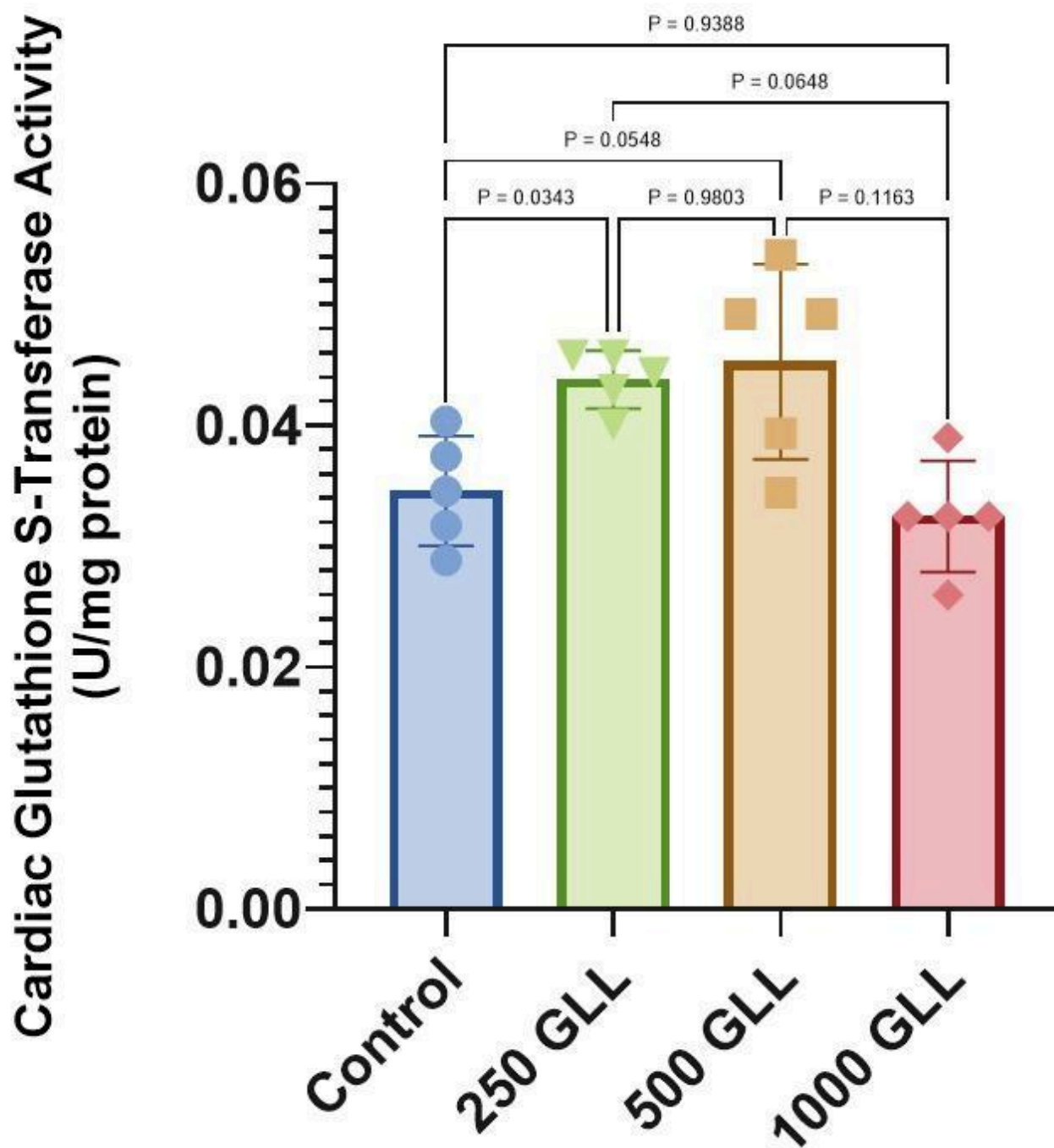


Figure 3

Effect of *Gongronema Latifolium* Methanolic Leaf Extract on Cardiac Glutathione S-Transferase Activity; Results are expressed as mean $\pm$ SD (n = 5) and analysed using a one-way ANOVA and Tukey's multiple comparisons test. GLL: *Gongronema Latifolium* Methanolic Leaf Extract.

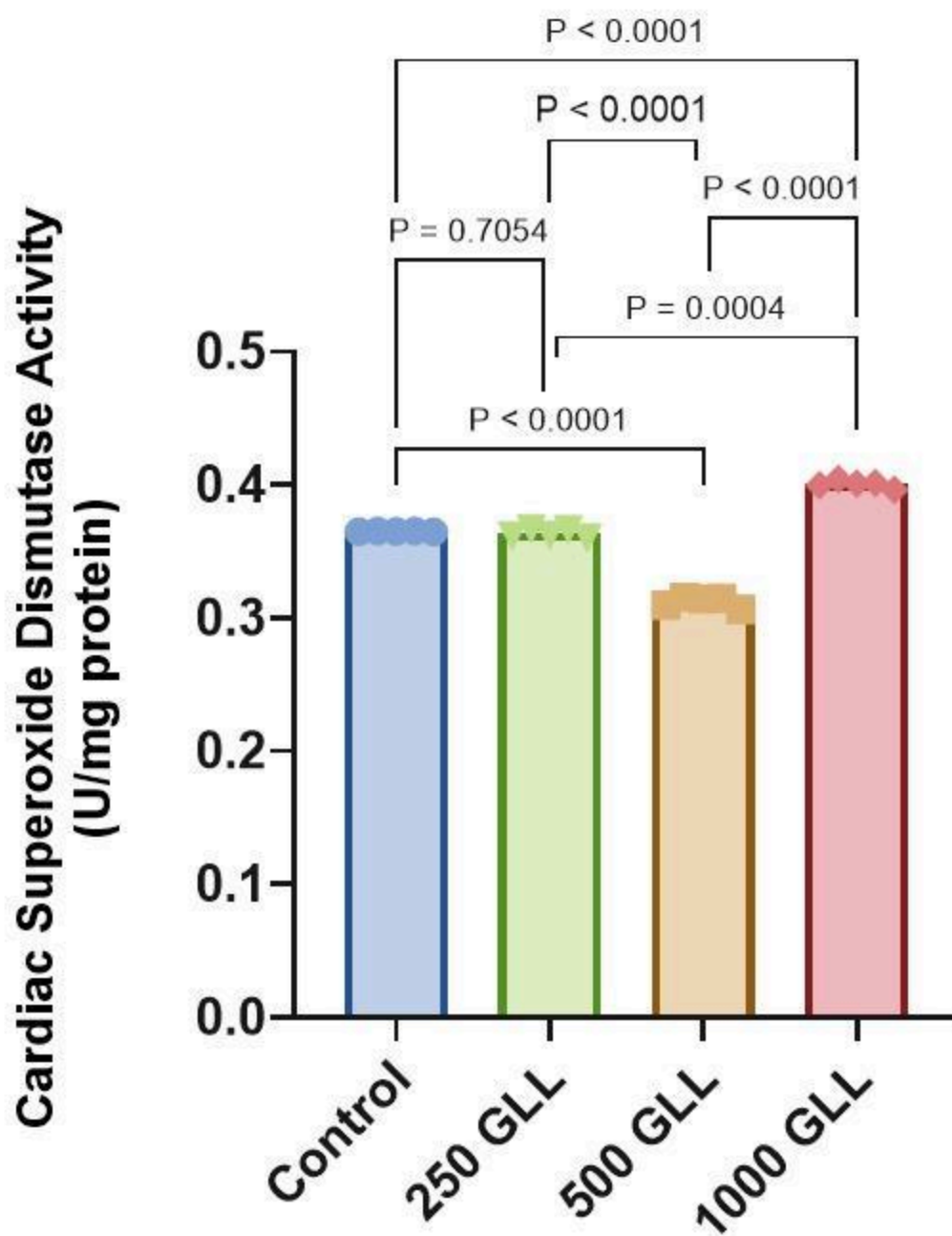


Figure 4

Effect of *Gongronema latifolium* Methanolic Leaf Extract on Cardiac Superoxide Dismutase Activity; Results are expressed as mean $\pm$ SD (n = 5) and analysed using a one-way ANOVA and Tukey's multiple comparisons test. GLL: *Gongronema Latifolium* Methanolic Leaf Extract.

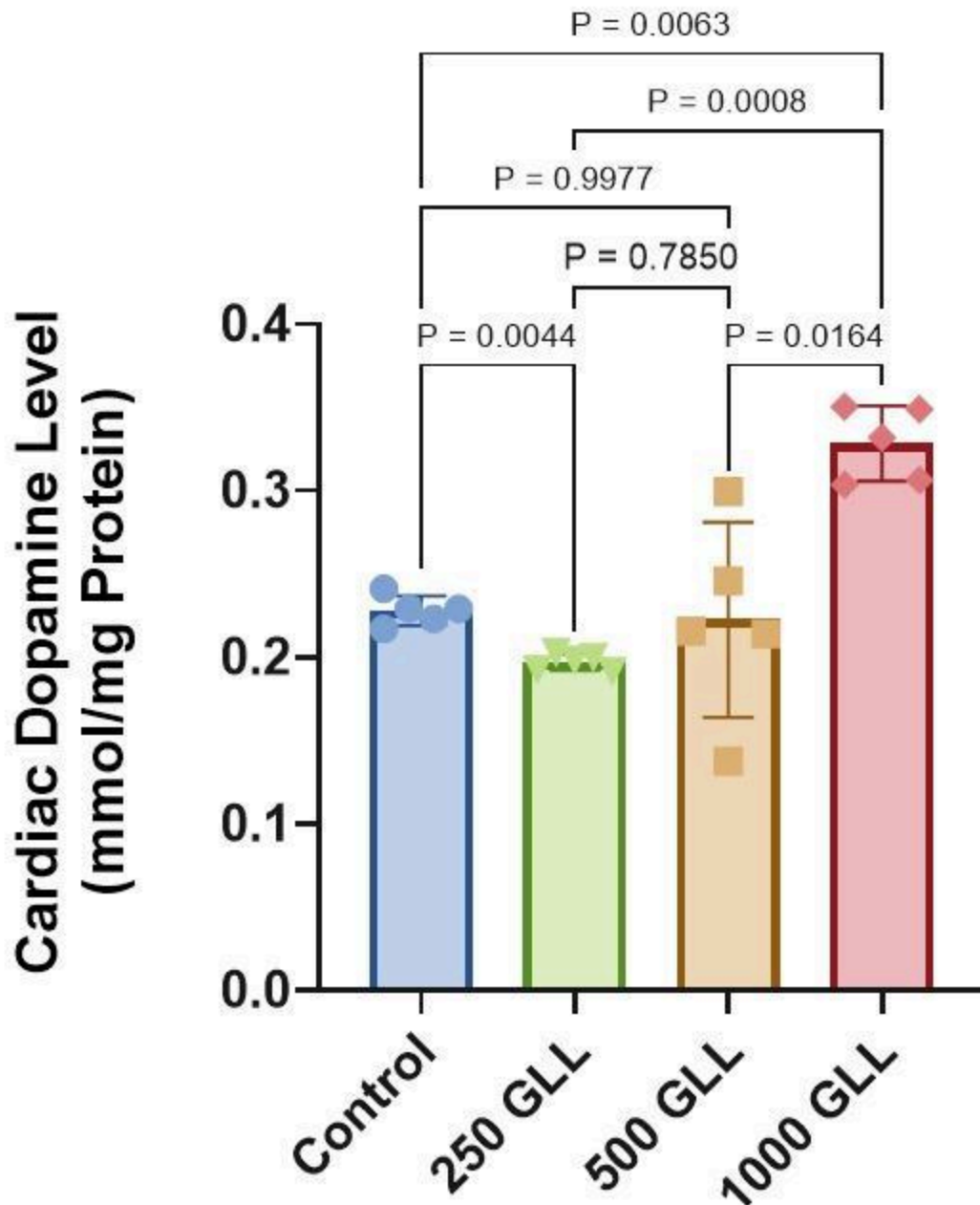


Figure 5

Effect of *Gongronema Latifolium* Methanolic Leaf Extract on Cardiac Dopamine Levels; Results are expressed as mean $\pm$ SD ($n = 5$) and analysed using a one-way ANOVA and Tukey's multiple comparisons tests. GLL: *Gongronema Latifolium* Methanolic Leaf Extract.