International Journal of Pharmaceutical and Bio-Medical Science

ISSN(print): 2767-827X, ISSN(online): 2767-830X

Volume 06 Issue 02 February 2026

Page No : 754-760

DOI: https://doi.org/10.47191/ijpbms/v6-i2-12, Impact Factor: 8.163

Effect of Hydro-Methanolic Extract of Macadamia Integrifolia Nuts on Oxidative Stress and Inflammatory Markers in Male Wistar Rats

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ABSTRACT

Background: Oxidative stress and inflammation contribute to the pathogenesis of several chronic diseases. Bioactive compounds in tree nuts, including Macadamia integrifolia, may influence redox balance and inflammatory signalling. This study evaluated the effects of hydro-methanolic Macadamia integrifolia nut extract on oxidative stress and inflammatory markers in male Wistar rats.

Methods: Twenty-four male Wistar rats were randomly allocated into four groups (n = 6 per group): control, 250 mg/kg, 500 mg/kg, and 1000 mg/kg extract-treated groups. The extract was administered orally once daily for 28 days. At study completion, serum levels of catalase (CAT), superoxide dismutase (SOD), malondialdehyde (MDA), glutathione (GSH), glutathione peroxidase (GPx), tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), C-reactive protein (CRP), interleukin-10 (IL-10), and nuclear factor kappa B (NF-κB) were measured using standard spectrophotometric and ELISA methods. Statistical analysis was performed using one-way ANOVA with Tukey's post hoc test.

Results: CAT and SOD activities showed no significant differences across all groups ($p > 0.05$). MDA levels were also comparable between control and treated groups, indicating no significant change in lipid peroxidation. In contrast, GSH levels decreased progressively with increasing extract dose, with significant reductions observed in the 500 mg/kg and 1000 mg/kg groups compared with the control ($p < 0.05$). GPx activity followed a similar dose-dependent decline, with significant reductions in the medium- and high-dose groups ($p < 0.05$). For inflammatory markers, TNF-α and IL-6 concentrations did not differ significantly among groups ($p > 0.05$). However, CRP levels were significantly lower in the 500 mg/kg and 1000 mg/kg groups compared with the control ($p < 0.05$). IL-10 and NF-κB concentrations also decreased significantly in the medium- and high-dose groups ($p < 0.05$), demonstrating a dose-dependent modulation of inflammatory signalling pathways.

Conclusion: Hydro-methanolic Macadamia integrifolia extract exerted selective, dose-dependent effects on glutathione-related antioxidant systems and inflammatory biomarkers without altering primary enzymatic antioxidants or lipid peroxidation.

ARTICLE DETAILS

Published On:
21 February 2026

KEYWORDS: Macadamia integrifolia; oxidative stress; inflammation; antioxidants; Wistar rats; glutathione.

Available on:
https://ijpbms.com/

1. INTRODUCTION

Oxidative stress reflects an imbalance between the generation of reactive oxygen species (ROS) and the capacity of endogenous antioxidant defence systems to neutralise them. Excessive ROS production contributes to lipid peroxidation, protein oxidation, DNA damage, and cellular dysfunction, processes implicated in the pathogenesis of cardiometabolic diseases, neurodegeneration, and ageing (Sies et al., 2017). Oxidative stress and inflammation are central features in the pathogenesis of many chronic diseases, including

cardiometabolic disorders, neurodegeneration, and cancer (Rajaram et al., 2023). Oxidative stress arises when there is an imbalance between pro-oxidant generation of reactive oxygen species (ROS) and the capacity of endogenous antioxidant systems such as catalase (CAT), superoxide dismutase (SOD), glutathione (GSH) and glutathione peroxidase (GPx) to neutralise them (Rajaram et al., 2023). Under sustained oxidative challenge, lipid peroxidation products such as malondialdehyde (MDA) accumulate, and chronic low-grade inflammation is maintained through upregulation of pro-inflammatory signalling pathways, including nuclear factor kappa B (NF-κB)–mediated cytokine production (Rajaram et al., 2023). Consequently, both oxidative and inflammatory processes are viable targets for dietary or pharmacological modulation in disease prevention and therapy.

In experimental and clinical settings, biomarkers such as malondialdehyde (MDA), reduced glutathione (GSH), superoxide dismutase (SOD), and catalase are widely used to assess oxidative status and antioxidant capacity (Yilgor & Demir, 2024). Because oxidative stress plays a central role in disease initiation and progression, strategies aimed at enhancing antioxidant defence mechanisms remain of considerable scientific and therapeutic interest.

Dietary factors substantially influence oxidative balance (Jiang et al., 2021). Diets rich in plant-derived antioxidants have been associated with reduced oxidative damage and improved metabolic outcomes (Kalogerakou & Antoniadou, 2024). Polyphenols, tocopherols, carotenoids, and unsaturated fatty acids exert antioxidant effects either directly through free radical scavenging or indirectly by modulating redox-sensitive transcription factors such as nuclear factor erythroid 2–related factor 2 (Nrf2) (Altanam et al., 2025; Andres et al., 2024). Activation of Nrf2 upregulates endogenous antioxidant enzymes, including SOD, catalase, and glutathione peroxidase, thereby strengthening cellular resilience against oxidative injury (Altanam et al., 2025; Andres et al., 2024). Consequently, plant-based functional foods have attracted increasing attention as potential modulators of systemic oxidative stress.

Tree nuts are nutrient-dense foods consistently associated with cardiometabolic benefits. Meta-analyses indicate that regular nut consumption improves lipid profiles and reduces inflammatory and oxidative biomarkers (Houston et al., 2023). These protective effects are largely attributed to their high content of monounsaturated and polyunsaturated fatty acids, fibre, tocopherols, and polyphenolic compounds (Mititelu et al., 2024). Beyond lipid modulation, nut-derived bioactives may enhance antioxidant enzyme activity and reduce lipid peroxidation, mechanisms closely linked to the attenuation of oxidative stress. Macadamia integrifolia nuts are distinguished by their particularly high concentration of monounsaturated fatty acids, especially oleic and palmitoleic acids, alongside significant levels of phenolic antioxidants and vitamin E compounds (Hung et al., 2023). Monounsaturated fatty acids have been shown to exert anti-inflammatory and antioxidative effects, partly through modulation of redox-sensitive signalling pathways (Santa-Maria et al., 2023). Phenolic constituents, in turn, can directly scavenge free radicals and enhance endogenous antioxidant systems (Platzer et al., 2022). Despite these promising bioactive properties, research on *Macadamia integrifolia* nuts has largely focused on lipid metabolism and glycaemic control, with limited experimental evaluation of their effects on oxidative stress biomarkers.

Given that oxidative stress and inflammation jointly contribute to systemic metabolic dysregulation, it is important to understand the effects of *Macadamia integrifolia* nut extract on redox homeostasis. Therefore, this study investigated the effects of the hydro-methanolic extract of *Macadamia integrifolia* nuts on oxidative stress and inflammatory markers in male Wistar rats.

2. MATERIALS AND METHODS

2.1 Study Design

This experiment was a controlled experimental study designed to evaluate the effects of hydro-methanolic extract of Macadamia integrifolia nuts on oxidative stress markers in male Wistar rats over a 28-day treatment period.

2.2 Study Area/Location

The experiment was conducted at the Animal House and Physiology Laboratory, Department of Physiology, College of Medical Sciences, Rivers State University, Port Harcourt, Nigeria.

2.3 Experimental Animals

Twenty-four (24) healthy adult male Wistar rats weighing 140–160 g were obtained from an accredited animal breeding facility in Port Harcourt, Nigeria. The Wistar rats were housed in ventilated polypropylene cages under controlled conditions (temperature 25 ± 2 °C, relative humidity 50–60%, 12-h light/dark cycle) and provided standard rat chow and water ad libitum. Rats were acclimatised for two weeks before experimentation. All procedures were conducted in accordance with the NIH Guide for the Care and Use of Laboratory Animals guidelines (National Institutes of Health, 2011).

2.4 Plant Material and Extract Preparation

Fresh nuts of *Macadamia integrifolia* were collected from Jos, Plateau State, Nigeria, authenticated by a taxonomist in the Department of Plant Science and Biotechnology, Rivers State University, and deposited as voucher specimen RSUPbH0259. Fresh Macadamia integrifolia nuts were cleaned, air-dried, and pulverised into fine paste. The paste sample was extracted using hydro-methanol (80% methanol in distilled water) by maceration for 72 hours with intermittent shaking. The mixture was filtered using Whatman No. 1 filter paper, and the filtrate was concentrated under reduced pressure using a rotary evaporator at 40°C. The

semi-solid extract was further dried in a water bath to obtain a stable crude extract and stored at 4°C until use.

2.5 Experimental Grouping and Treatment

Wistar rats were randomly assigned to four groups (n = 6 per group):

Group 1 (Control): Received distilled water.

Group 2 (Low dose): Received 250 mg/kg hydromethanolic extract of *Macademia Integrifolia* nuts.

Group 3 (Medium dose): Received 500 mg/kg hydromethanolic extract of *Macademia Integrifolia* nuts.

Group 4 (High dose): Received 1000 mg/kg hydromethanolic extract of *Macademia Integrifolia* nuts.

Treatments were administered orally by gavage once daily for 28 consecutive days, in accordance with OECD Test No. 423 for the acute oral toxicity study (OECD, 2002).

2.6 Sample Collection

At the end of the treatment period, the animals were fasted overnight and euthanised under mild anaesthesia. Blood samples were collected via cardiac puncture into plain tubes and centrifuged at 3000 rpm for 10 minutes to obtain serum. The serum samples were stored at −20°C until biochemical analysis.

2.7 Determination of Oxidative Stress Markers

Serum catalase (CAT) activity was determined using a spectrophotometric method based on the decomposition of hydrogen peroxide. Superoxide dismutase (SOD) activity was measured by its ability to inhibit auto-oxidation reactions. Malondialdehyde (MDA), an index of lipid peroxidation, was quantified using the thiobarbituric acid reactive substances (TBARS) method. Reduced glutathione (GSH) levels were determined using Ellman's reagent (5,5′-dithiobis-2-nitrobenzoic acid). Glutathione peroxidase (GPx) activity was assessed based on its catalytic conversion of reduced glutathione in the presence of hydrogen peroxide. All enzyme activities and oxidative stress parameters were expressed per mg of protein. Protein concentration was determined using a standard protein assay method.

2.8 Determination of Oxidative Stress Markers

Serum inflammatory markers were quantified using commercially available enzyme-linked immunosorbent assay (ELISA) kits specific for rat cytokines, following the manufacturer's instructions. The inflammatory parameters assessed included tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-10 (IL-10), C-reactive protein (CRP), and nuclear factor kappa B (NF-κB). Briefly, serum samples previously stored at −20°C were thawed on ice and centrifuged to remove debris before analysis. Standards and samples were added in duplicate to pre-coated 96-well microplates and incubated to allow antigen–antibody binding. After washing to remove unbound substances, biotinylated detection antibodies were added, followed by streptavidin–horseradish peroxidase conjugate. The reaction was developed using tetramethylbenzidine (TMB) substrate solution and stopped with sulfuric acid. Optical density was measured at 450 nm using a microplate reader. Concentrations of TNF-α, IL-6, IL-10, CRP, and NF-κB were calculated from standard calibration curves generated using known concentrations provided in the kits. Results were expressed as pg/mg protein, ng/mg protein, or mg/L as appropriate. All assays were performed in accordance with quality control procedures to ensure intra- and inter-assay precision. Protein concentration of serum samples was determined using a standard protein assay method, and inflammatory marker levels were normalised to total protein where applicable.

2.9 Statistical Analysis

Data were expressed as mean ± standard error of the mean (SEM) for six animals per group. Statistical analysis was performed using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test for multiple comparisons. Differences were considered statistically significant at $p < 0.05$. Analyses were performed using R version 4.3.3 (R Core Team, 2024).

3. RESULTS

3.1 Oxidative Stress Markers

The effects of hydro-methanolic *Macadamia integrifolia* nuts extract on oxidative stress markers in Wistar rats are presented in **Table 1**. Catalase (CAT) activity ranged from 2.00 ± 0.07 to 2.10 ± 0.05 U/mg across all treatment groups, with no significant differences observed ($p > 0.05$). Similarly, superoxide dismutase (SOD) activity and malondialdehyde (MDA) levels were comparable between groups ($P > 0.05$). Glutathione (GSH) concentration decreased progressively with increasing extract dose, with the low-dose (1.85 ± 0.05 µmol/mg), medium-dose (1.70 ± 0.04 µmol/mg), and high-dose (1.52 ± 0.06 µmol/mg) groups showing statistically lower values than control (2.09 ± 0.03 µmol/mg; $p < 0.05$). Glutathione peroxidase (GPx) activity also declined significantly in the medium- (0.04 ± 0.00 U/mg) and high-dose (0.03 ± 0.00 U/mg) groups relative to control (0.05 ± 0.00 U/mg; $P < 0.05$), while the low-dose group showed a non-significant reduction (0.04 ± 0.00 U/mg).

Table 1. Oxidative stress markers of Wistar rats after 28 days of treatment with hydro-methanolic *Macadamia integrifolia* nuts extract

Parameter (n=6)	Control	Low dose (250 mg/kg)	Medium dose (500 mg/kg)	High dose (1000 mg/kg)
CAT (U/mg)	2.10 ± 0.05[a]	2.05 ± 0.06[a]	2.00 ± 0.07[a]	2.02 ± 0.05[a]
SOD (U/mg)	1.50 ± 0.04[a]	1.48 ± 0.05[a]	1.45 ± 0.06[a]	1.47 ± 0.05[a]

MDA (nmol/mg)	3.20 ± 0.10^{a}	3.25 ± 0.12^{a}	3.30 ± 0.11^{a}	3.28 ± 0.09^{a}
GSH (µmol/mg)	2.09 ± 0.03^{a}	1.85 ± 0.05^{ab}	1.70 ± 0.04^{b}	1.52 ± 0.06^{b}
GPx (U/mg)	0.05 ± 0.00^{a}	0.04 ± 0.00^{ab}	0.04 ± 0.00^{b}	0.03 ± 0.00^{b}

Values are presented as mean ± SEM (n = 6). Superscripts (a, b, c) indicate statistically significant differences between groups at $p < 0.05$ (ANOVA followed by Tukey's post hoc test). Groups sharing the same superscript are not significantly different. GSH: Glutathione; GPX: Glutathione peroxidase; CAT: Catalase; SOD: Superoxide dismutase; MDA: Malondialdehyde.

3.2 Inflammatory Markers

Table 2 summarises the inflammatory marker profiles of Wistar rats following 28 days of treatment. Tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) levels were similar across all groups ($P > 0.05$). C-reactive protein (CRP) decreased significantly in the medium- (2.50 ± 0.07 mg/L) and high-dose (2.30 ± 0.06 mg/L) groups compared with control (2.80 ± 0.09 mg/L; $P < 0.05$), while the low-dose group (2.65 ± 0.08 mg/L) did not differ significantly from control. Interleukin-10 (IL-10) levels also declined dose-dependently, with significant reductions observed in the medium- (11.80 ± 0.35 pg/mg) and high-dose (11.50 ± 0.32 pg/mg) groups compared with control (12.40 ± 0.40 pg/mg; $P < 0.05$). Nuclear factor kappa B (NF-κB) concentration showed a similar pattern, decreasing significantly in the medium- (1.15 ± 0.03 ng/mg) and high-dose (1.10 ± 0.04 ng/mg) groups relative to control (1.20 ± 0.03 ng/mg; $P < 0.05$).

Table 2. Inflammatory markers of Wistar rats after 28 days of treatment with hydro-methanolic Macadamia integrifolia nuts extract

Parameter (n=6)	Control	Low dose (250 mg/kg)	Medium dose (500 mg/kg)	High dose (1000 mg/kg)
TNF-α (pg/mg)	25.10 ± 0.80^{a}	24.85 ± 0.75^{a}	24.40 ± 0.70^{a}	24.60 ± 0.78^{a}
IL-6 (pg/mg)	18.50 ± 0.60^{a}	18.20 ± 0.55^{a}	17.95 ± 0.62^{a}	18.10 ± 0.58^{a}
CRP (mg/L)	2.80 ± 0.09^{a}	2.65 ± 0.08^{ab}	2.50 ± 0.07^{b}	2.30 ± 0.06^{b}
IL-10 (pg/mg)	12.40 ± 0.40^{a}	12.10 ± 0.38^{ab}	11.80 ± 0.35^{b}	11.50 ± 0.32^{b}
NF-κB (ng/mg)	1.20 ± 0.03^{a}	1.18 ± 0.04^{ab}	1.15 ± 0.03^{b}	1.10 ± 0.04^{b}

Values are presented as mean ± SEM (n = 6). Superscripts (a, b) indicate statistically significant differences between groups at $p < 0.05$ (ANOVA followed by Tukey's post hoc test). Groups sharing the same superscript are not significantly different. TNF-α: Tumour necrosis factor-alpha; IL-6: Interleukin-6; IL-10: Interleukin-10; CRP: C-reactive protein; NF-κB: Nuclear factor kappa B.

4. DISCUSSION

The present study investigated the effects of hydro-methanolic extract of macadamia nuts on oxidative stress markers in adult Wistar rats. The findings revealed dose-dependent oxidative stress markers, with low doses exerting adverse metabolic effects, whereas high doses demonstrated protective effects. The findings from this study highlight the potential beneficial role of macadamia nuts in the modulation of oxidative stress and antioxidant markers. In this study, the effects of hydro-methanolic Macadamia integrifolia nuts extract on oxidative stress and inflammatory markers in Wistar rats were evaluated over a 28-day period. Oxidative stress plays a central role in metabolic and cardiovascular disorders (Dubois-Deruy et al., 2020).

The results demonstrate that while primary enzymatic antioxidants such as catalase (CAT) and superoxide dismutase (SOD) were largely unaffected by the extract, non-enzymatic antioxidant levels (GSH) and glutathione peroxidase (GPx) activity decreased significantly in medium- and high-dose groups. These findings suggest that prolonged or higher-dose exposure to macadamia nut extract may selectively modulate components of the antioxidant defence system. This finding contrasts with Zhang et al. (2024), who reported enhanced antioxidant activity following macadamia oil supplementation in high-fat diet-induced rats, mediated via activation of the AMPK/Nrf2 pathway (Camacho-Teodocio et al., 2024; Zhang et al., 2024). Similarly, El-Hawary et al. (2022) observed increased antioxidant enzyme activity in rats treated with macadamia extracts (Camacho-Teodocio et al., 2024; Seham El-Hawary, 2022). The discrepancy may be attributed to differences in extract composition (oil vs. hydro-methanol extract), treatment duration, or dosage. Our results suggest that while macadamia extracts confer lipid-lowering benefits, higher doses may deplete endogenous antioxidant reserves, warranting further mechanistic investigation. Therefore, reductions in these markers may indicate increased utilisation in response to oxidative challenges or transient suppression due to bioactive interactions (Halliwell & Gutteridge, 2015). The absence of significant changes in CAT, SOD, and MDA suggests that lipid peroxidation and primary enzymatic defences remained largely uncompromised, highlighting a selective modulatory effect rather than a general pro-oxidant impact.

Furthermore, regarding inflammatory markers, TNF-α and IL-6 were not significantly altered across the groups, indicating that the extract did not provoke systemic pro-inflammatory signalling. However, dose-dependent

reductions were observed in CRP, IL-10, and NF-κB levels, particularly in the medium- and high-dose groups. CRP, a sensitive acute-phase protein, reflects systemic inflammatory status, while NF-κB is a master transcriptional regulator of pro-inflammatory cytokines (Lawrence, 2009). The observed decreases suggest that hydro-methanolic macadamia nut extract may exert mild anti-inflammatory effects, possibly mediated through modulation of intracellular signalling pathways that control cytokine production. Interestingly, the reduction in IL-10, an anti-inflammatory cytokine, may reflect a compensatory response to decreased pro-inflammatory signalling, consistent with previous studies showing that balanced cytokine regulation occurs when inflammation is suppressed (Saraiva & O'Garra, 2010).

The selective modulation of oxidative stress and inflammatory markers by Macadamia integrifolia extract may be attributed to its bioactive composition. Macadamia nuts are rich in monounsaturated fatty acids, vitamin E, and phenolic compounds (Tu et al., 2021), which have been demonstrated to scavenge free radicals, inhibit NF-κB activation, and reduce systemic inflammation in experimental models (Jiang et al., 2006; Ros, 2010). These bioactive compounds likely contributed to the observed decline in CRP and NF-κB, without triggering overt oxidative damage as reflected by stable MDA levels. The differential effects on enzymatic and non-enzymatic antioxidants underscore the complexity of phytochemical interactions in vivo and highlight the need to consider dose-dependent responses when evaluating functional foods.

These findings indicate that hydro-methanolic *Macadamia integrifolia* nuts extract exerts a mild anti-inflammatory effect while selectively modulating antioxidant defences, particularly GSH and GPx. This dual action—supporting inflammatory balance while modulating oxidative capacity—may have implications for cardiometabolic health, given the central roles of oxidative stress and inflammation in disease pathogenesis. Future studies should investigate the mechanistic pathways underpinning these effects, including redox-sensitive signalling networks and dose-response relationships, to delineate safe and efficacious consumption levels for therapeutic or preventive applications.

5. CONCLUSION

Hydro-methanolic extract of Macadamia integrifolia nuts demonstrated selective modulatory effects on oxidative stress and inflammatory markers in male Wistar rats. While primary enzymatic antioxidants (CAT, SOD) and lipid peroxidation (MDA) remained unchanged, non-enzymatic antioxidants (GSH) and GPx activity declined in a dose-dependent manner, indicating targeted modulation of redox homeostasis. Concurrently, inflammatory markers such as CRP and NF-κB decreased at medium and high doses, suggesting mild anti-inflammatory effects without provoking systemic pro-inflammatory responses. These findings highlight the potential of Macadamia integrifolia bioactives to support inflammatory balance while influencing antioxidant capacity, providing a basis for further investigations into their therapeutic or preventive applications in oxidative stress–related and inflammatory conditions.

ACKNOWLEDGEMENTS

We extend our deepest gratitude to the staff of the Department of Human Physiology, Rivers State University, Port Harcourt, Nigeria, and Mr Barine Roja, Ms Praise and Victory, whose technical support was instrumental in the successful execution of this study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

AUTHORS' CONTRIBUTIONS

Edith Reuben designed the research methodology and performed the experiments, analysed the data, and drafted the first manuscript. Nimisoere P Batubo and Boma H Opusunju reviewed the manuscript. Bright Ichechi Owhorji provided critical and analytical feedback. Edith Reuben, Nimisoere P Batubo, Boma H Opusunju and Bright Ichechi Owhorji revised the manuscript. All authors approved the final manuscript.

ETHICS APPROVAL

All experimental procedures received approval from the Research Ethics Committee at the University of Port Harcourt (Approval No: UPH/CERMAD/REC/MM90/216). Animal handling and protocols adhered to the NIH Guide for the Care and Use of Laboratory Animals (8th edition). The study also followed the ARRIVE 2.0 guidelines for reporting animal research. Measures were taken to minimise animal suffering, reduce the number of animals used, and refine procedures in line with the 3Rs principles (Replacement, Reduction, and Refinement) (National Institutes of Health, 2011).

REFERENCES

I. Altanam, S. Y., Darwish, N., & Bakillah, A. (2025). Exploring the Interplay of Antioxidants, Inflammation, and Oxidative Stress: Mechanisms, Therapeutic Potential, and Clinical Implications. *Diseases*, *13*(9).https://doi.org/10.3390/diseases13090309

II. Andres, C. M. C., Perez de la Lastra, J. M., Juan, C. A., Plou, F. J., & Perez-Lebena, E. (2024). Antioxidant Metabolism Pathways in Vitamins, Polyphenols, and Selenium: Parallels and Divergences. *Int J Mol Sci*, *25*(5).https://doi.org/10.3390/ijms25052600

III. Camacho-Teodocio, J. D., Gallardo-Velázquez, T., Osorio-Revilla, G., Castañeda-Pérez, E., Velázquez-

Contreras, C., Cornejo-Mazón, M., & Hernández-Martínez, D. M. (2024). Macadamia (Macadamia integrifolia) Nut-Based Beverage: Physicochemical Stability and Nutritional and Antioxidant Properties. *Beverages*, *10*(3), 58. https://www.mdpi.com/2306-5710/10/3/58

IV. Dubois-Deruy, E., Peugnet, V., Turkieh, A., & Pinet, F. (2020). Oxidative Stress in Cardiovascular Diseases. *Antioxidants (Basel)*, *9*(9).https://doi.org/10.3390/antiox9090864

V. Houston, L., Probst, Y. C., Chandra Singh, M., & Neale, E. P. (2023). Tree Nut and Peanut Consumption and Risk of Cardiovascular Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Adv Nutr*, *14*(5), 1029-1049. https://doi.org/10.1016/j.advnut.2023.05.004

VI. Hung, H. C., Tsai, S. F., Chou, H. W., Tsai, M. J., Hsu, P. L., & Kuo, Y. M. (2023). Dietary fatty acids differentially affect secretion of pro-inflammatory cytokines in human THP-1 monocytes. *Sci Rep*, *13*(1), 5511. https://doi.org/10.1038/s41598-023-32710-5

VII. Jiang, R., Jacobs, D. R., Jr., Mayer-Davis, E., Szklo, M., Herrington, D., Jenny, N. S., Kronmal, R., & Barr, R. G. (2006). Nut and seed consumption and inflammatory markers in the multi-ethnic study of atherosclerosis. *Am J Epidemiol*, *163*(3), 222-231. https://doi.org/10.1093/aje/kwj033

VIII. Jiang, S., Liu, H., & Li, C. (2021). Dietary Regulation of Oxidative Stress in Chronic Metabolic Diseases. *Foods*, *10*(8). https://doi.org/10.3390/foods10081854

IX. Kalogerakou, T., & Antoniadou, M. (2024). The Role of Dietary Antioxidants, Food Supplements and Functional Foods for Energy Enhancement in Healthcare Professionals. *Antioxidants (Basel)*, *13*(12). https://doi.org/10.3390/antiox13121508

X. Lawrence, T. (2009). The nuclear factor NF-kappaB pathway in inflammation. *Cold Spring Harb Perspect Biol*, *1*(6), a001651. https://doi.org/10.1101/cshperspect.a001651

XI. Mititelu, M., Lupuliasa, D., Neacsu, S. M., Olteanu, G., Busnatu, S. S., Mihai, A., Popovici, V., Maru, N., Boroghina, S. C., Mihai, S., Ionita-Mindrican, C. B., & Scafa-Udriste, A. (2024). Polyunsaturated Fatty Acids and Human Health: A Key to Modern Nutritional Balance in Association with Polyphenolic Compounds from Food Sources. *Foods*, *14*(1). https://doi.org/10.3390/foods14010046

XII. National Institutes of Health. (2011). National Research Council (US) Committee for the Update of the Guide for the Care and Use of Laboratory Animals. In *Guide for the Care and Use of Laboratory Animals* (8th ed.). https://doi.org/10.17226/12910

XIII. OECD. (2002). *Test No. 423: Acute Oral toxicity - Acute Toxic Class Method, OECD Guidelines for the Testing of Chemicals*. P. OECD Publishing.

XIV. Platzer, M., Kiese, S., Tybussek, T., Herfellner, T., Schneider, F., Schweiggert-Weisz, U., & Eisner, P. (2022). Radical Scavenging Mechanisms of Phenolic Compounds: A Quantitative Structure-Property Relationship (QSPR) Study. *Front Nutr*, *9*, 882458. https://doi.org/10.3389/fnut.2022.882458

XV. R Core Team. (2024). *_R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing*. In (Version 4.4.2) Vienna, Austria. https://www.R-project.org/.

XVI. Rajaram, S., Damasceno, N. R. T., Braga, R. A. M., Martinez, R., Kris-Etherton, P., & Sala-Vila, A. (2023). Effect of Nuts on Markers of Inflammation and Oxidative Stress: A Narrative Review. *Nutrients*, *15*(5). https://doi.org/10.3390/nu15051099

XVII. Ros, E. (2010). Health benefits of nut consumption. *Nutrients*, *2*(7), 652-682. https://doi.org/10.3390/nu2070652

XVIII. Santa-Maria, C., Lopez-Enriquez, S., Montserrat-de la Paz, S., Geniz, I., Reyes-Quiroz, M. E., Moreno, M., Palomares, F., Sobrino, F., & Alba, G. (2023). Update on Anti-Inflammatory Molecular Mechanisms Induced by Oleic Acid. *Nutrients*, *15*(1). https://doi.org/10.3390/nu15010224

XIX. Saraiva, M., & O'Garra, A. (2010). The regulation of IL-10 production by immune cells. *Nat Rev Immunol*, *10*(3), 170-181.https://doi.org/10.1038/nri2711

XX. Seham El-Hawary, M. A., Engy A. Mahrous, . (2022). Extracts of different organs of Macadamia integrifolia ameliorate oxidative damage in a D-galactose accelerated ageing model in rats. . *Biointerface Research in Applied Chemistry*, *12*(5), 7125-7135. https://doi.org/https://doi.org/10.33263/BRIAC125.71257135

XXI. Sies, H., Berndt, C., & Jones, D. P. (2017). Oxidative Stress. *Annu Rev Biochem*, *86*, 715-748. https://doi.org/10.1146/annurev-biochem-061516-045037

XXII. Tu, X. H., Wu, B. F., Xie, Y., Xu, S. L., Wu, Z. Y., Lv, X., Wei, F., Du, L. Q., & Chen, H. (2021). A comprehensive study of raw and roasted macadamia nuts: Lipid profile, physicochemical, nutritional, and sensory properties. *Food Sci Nutr*, *9*(3), 1688-1697. https://doi.org/10.1002/fsn3.2143

XXIII. Yilgor, A., & Demir, C. (2024). Determination of oxidative stress level and some antioxidant activities in refractory epilepsy patients. *Sci Rep*, *14*(1), 6688. https://doi.org/10.1038/s41598-024-57224-6

XXIV. Zhang, M., Zhang, Y., Li, L., Wei, C., Dai, T., Li, Y., Shuai, X., & Du, L. (2024). Macadamia (Macadamia integrifolia) Oil Prevents High-Fat Diet-Induced Lipid Accumulation and Oxidative Stress by Activating the AMPK/Nrf2 Pathway. *Foods*, *13*(22). https://doi.org/10.3390/foods13223672