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Preparation of Physalis Angulata Water Extract with High Antioxidant Efficacy and Preliminary Toxicological Assessment

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ABSTRACT

Physalis angulata L. is traditionally used for various medicinal purposes; however, its antioxidant efficacy and safety profile remain insufficiently validated. This study aimed to optimize aqueous extraction conditions to obtain an extract with high antioxidant activity and to evaluate its preliminary toxicity. Dried plant material was extracted using water at different temperatures (40–100 °C) and extraction times (15 min–3 h). Antioxidant activity was assessed using DPPH radical scavenging, ferric reducing antioxidant power (FRAP), total phenolic content (TPC), and malondialdehyde (MDA) inhibition assays, while phytochemical profiling was performed using HPLC. Toxicity was evaluated using the brine shrimp lethality test (BSLT) and acute oral toxicity in rats. Extraction at 80 °C for 30 min exhibited the highest DPPH inhibition and TPC, while optimal FRAP values were observed at 60–80 °C for 1 h. The lowest MDA levels were recorded at 100 °C for 2 h. HPLC analysis identified chlorogenic acid and rutin as the major phenolic constituents. The extract demonstrated low toxicity in the BSLT, with significant lethality only at high concentrations, and no mortality or adverse effects were observed in rats following acute oral administration. In conclusion, optimized aqueous extracts of *P. angulata* exhibit strong antioxidant activity with a favorable preliminary safety profile, supporting their potential application as a natural antioxidant source for further development.

Keywords: Physalis angulata, extraction optimization, phenolic compounds, HPLC, antioxidant activity, acute toxicity

INTRODUCTION

Natural products derived from medicinal plants continue to attract significant scientific interest due to their long-standing traditional use and their potential as sources of bioactive compounds with health-promoting properties (El-Saadony *et al*., 2025). Among these, antioxidant-rich plant extracts have been extensively investigated for their ability to neutralize reactive oxygen species (ROS), which are implicated in the pathogenesis of various chronic diseases, including cardiovascular disorders, diabetes, neurodegenerative diseases, and cancer (Muscolo *et al*., 2024). Consequently, the identification and optimization of plant-based antioxidants, together with an evaluation of their safety, remain an important area of research.

Physalis angulata L., a member of the Solanaceae family, is an annual herb widely distributed in tropical and subtropical regions (Ramakrishna *et al*., 2022). In Malaysia, it is commonly known as "letup-letup" and has been traditionally used for various medicinal purposes, including as a sedative, depurative, anti-rheumatic agent, and for the relief of earache (Lem *et al*., 2022). Ethnomedicinal reports have also described its use in the management of inflammation, pain, and metabolic disorders (Novitasari *et al*., 2024). Despite its extensive traditional application, scientific studies validating its antioxidant potential and safety profile are still relatively limited.

Previous pharmacological investigations have demonstrated that *P. angulata* exhibits anti-inflammatory, antinociceptive, antipyretic, and antidiabetic activities, suggesting the presence of bioactive phytochemicals with significant therapeutic potential (Tuan Anh *et al*., 2021). Phytochemical studies have reported that *P. angulata* contains various secondary metabolites, including physalins, withanolides, flavonoids, and phenolic acids, which are known contributors to antioxidant activity (Pillai *et al*., 2024).

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The antioxidant efficacy of plant extracts is strongly influenced by extraction parameters, including solvent type, temperature, and extraction duration (Xu *et al*., 2017). Aqueous extraction is especially relevant for traditional medicinal use and food-related applications; however, inappropriate extraction conditions may lead to suboptimal recovery of bioactive compounds or degradation of thermolabile constituents (Zhang *et al*., 2018). Therefore, optimizing extraction temperature and time is crucial to maximize antioxidant activity while preserving compound stability.

In addition to bioactivity, safety evaluation is a fundamental requirement in the early development of plant-based products (Najmi *et al*., 2022). Preliminary toxicity screening methods, such as the brine shrimp lethality test, provide a rapid and cost-effective approach for assessing potential cytotoxicity and guiding subsequent in vivo safety studies (Banti *et al*., 2021). Although *P. angulata* has been traditionally consumed, systematic toxicological data supporting its safe use remain scarce, particularly for standardized extracts prepared under controlled conditions.

In this context, the present study aimed to prepare a *P. angulata* water extract with high antioxidant efficacy by optimizing extraction temperature and duration. The antioxidant properties of the extracts were evaluated using DPPH radical scavenging, ferric reducing antioxidant power (FRAP), total phenolic content (TPC), and malondialdehyde (MDA) inhibition assays. Furthermore, a preliminary toxicological assessment was conducted using the brine shrimp lethality test to provide an initial indication of extract safety. The findings of this study are expected to contribute valuable baseline data supporting the potential use of *P. angulata* as a natural antioxidant source and to guide future in vivo safety and efficacy investigations.

METHOD

Collection of plant and authentication

Physalis angulata L. whole plant was collected from the Forest Research Institute Malaysia (FRIM), Kepong, Selangor, Malaysia (3.2370° N, 101.6340° E). The collected specimen was taxonomically identified and authenticated by a qualified botanist from the Natural Product Division, FRIM. A voucher specimen was prepared and deposited at the FRIM Herbarium for future reference. The plant material was cleaned to remove soil and extraneous matter prior to further processing.

Preparation of water extract

The collected *P. angulata* plant material was thoroughly washed with distilled water to remove adhering impurities and air-dried prior to oven drying at 55 °C for 48 h until a constant weight was achieved. The dried material was then ground into a fine powder using a mechanical grinder and stored in an airtight container at room temperature until further use. For extraction, 0.5 g of powdered plant material was weighed and mixed with 10 mL of distilled water (solid-to-solvent ratio 1:20, w/v) in centrifuge tubes. The mixtures were subjected to thermal extraction using a temperature-controlled water bath at different temperatures (40, 60, 80, and 100 °C) and extraction times (15 min, 30 min, 1 h, 2 h, and 3 h). After extraction, the samples were allowed to cool to room temperature and subsequently centrifuged at 4000 rpm for 15 min to remove particulate matter. The supernatants were carefully collected and stored at −20 °C until further analysis. All extractions were performed in triplicate.

Antioxidant test

2,2-diphenyl-1-picrylhydrazyl (DPPH)

The DPPH radical scavenging activity was determined according to Abdullah *et al*. (2021) with slight modifications. A 0.1 mM DPPH solution was freshly prepared by dissolving 3.94 mg of DPPH in 100 mL of methanol and kept in the dark prior to use. Briefly, 50 µL of *P. angulata* extract was mixed with 100 µL of DPPH solution in a 96-well microplate. The reaction mixture was incubated in the dark at room temperature for 30 min. The absorbance was measured at 517 nm using a microplate reader. Ascorbic acid was used as a positive control at appropriate concentrations. Methanol with DPPH solution served as the negative control. All

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experiments were performed in triplicate. The percentage of DPPH radical scavenging activity was calculated using the following equation:

$$\% \text{ inhibition} = [(A_{control} - A_{sample}) / A_{control}] \times 100$$

Ferric Reducing Antioxidant Power (FRAP)

The ferric reducing antioxidant power (FRAP) assay was performed according to the method described by Benzie and Strain (1996) with slight modifications. The FRAP reagent was freshly prepared by mixing 10 mM TPTZ solution in 40 mM HCl, 20 mM $FeCl_3 \cdot 6H_2O$, and 300 mM acetate buffer (pH 3.6) in a ratio of 1:1:10 (v/v/v).

A standard calibration curve was prepared using $FeSO_4 \cdot 7H_2O$ at concentrations ranging from 0.1 to 2.0 mmol/L. For the assay, 30 µL of *P. angulata* extract was added to 200 µL of freshly prepared FRAP reagent in a 96-well microplate. The reaction mixture was incubated at 37 °C for 30 min, and the absorbance was measured at 593 nm using a microplate reader. Ascorbic acid was used as the positive control. All measurements were performed in triplicate. Results were expressed as µmol Fe^{2+} equivalents per gram of sample (µmol Fe^{2+}/g).

Total Phenolic Content (TPC)

The total phenolic content (TPC) of the extracts was determined using the Folin–Ciocalteu method as described by Singleton and Rossi (1965) with slight modifications. Briefly, 20 µL of *P. angulata* extract was mixed with 10 µL of Folin–Ciocalteu reagent in a 96-well microplate. The mixture was allowed to react for 5 min at room temperature. Subsequently, 40 µL of 7.5% (w/v) sodium carbonate solution was added, and the reaction mixture was incubated in the dark at room temperature for 2 h.

The absorbance was measured at 765 nm using a microplate reader. A standard calibration curve was prepared using gallic acid at appropriate concentrations. The total phenolic content was expressed as milligrams of gallic acid equivalents per gram of sample (mg GAE/g). All measurements were performed in triplicate.

Lipid peroxidation assay (MDA/TBARS)

Lipid peroxidation was evaluated using a modified thiobarbituric acid reactive substances (TBARS) assay as described by Upadhyay *et al*. (2014), using egg yolk homogenate as a lipid-rich medium. Briefly, 250 µL of 10% (v/v) egg yolk homogenate was mixed with 50 µL of *P. angulata* extract. Distilled water was added to adjust the total volume to 500 µL. Lipid peroxidation was initiated by adding 25 µL of 0.07 M $FeSO_4$, followed by incubation at room temperature for 30 min.

Subsequently, 750 µL of 0.8% (w/v) thiobarbituric acid (TBA), 750 µL of 20% (v/v) acetic acid (pH 3.5), and 25 µL of 20% (w/v) trichloroacetic acid (TCA) were added to the reaction mixture. The tubes were heated in a boiling water bath for 60 min and then cooled to room temperature. After cooling, 3.0 mL of n-butanol was added, and the mixture was centrifuged at 4000 rpm for 10 min. The absorbance of the upper organic layer was measured at 532 nm using a spectrophotometer. All experiments were performed in triplicate, and results were expressed as percentage inhibition of lipid peroxidation.

Preparation of P. angulata extract and HPLC analysis

Physalis angulata plant material was washed, oven-dried at 55 °C for 48 h, and ground into a fine powder. For large-scale extraction, 100 g of powdered sample was extracted with 1 L of distilled water (solid-to-solvent ratio 1:10, w/v) using a water bath at 100 °C for 1 h. The extract was allowed to cool, filtered to remove plant residues, and subsequently concentrated using a rotary evaporator at 55 °C under reduced pressure. The concentrated extract was stored at −20 °C prior to analysis.

HPLC analysis was performed according to Ekeke *et al*. (2019) with slight modifications. A Shimadzu LC-10 system equipped with an LC-10AD pump, CTO-10A column oven, SPD-10A UV–Vis detector, CBM-10A

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interface, and LC-10 workstation was used. Separation was carried out on a reversed-phase C18 column (250 mm × 4.6 mm i.d., 5 µm; Supelco, USA) maintained at 30 °C. The mobile phase consisted of acetonitrile and water (40:60, v/v) under isocratic conditions at a flow rate of 1.0 mL/min. The injection volume was 20 µL, and detection was performed at 274 nm. Identification and quantification of chlorogenic acid and rutin were carried out using external standards. Calibration curves were prepared at appropriate concentration ranges, and linearity was confirmed with correlation coefficients (R^2) greater than 0.99. Results were expressed as concentration (ppm) and percentage of compound in the extract (w/w).

Brine Shrimp Lethality Test (BSLT)

Preliminary cytotoxicity of *P. angulata* extract was evaluated using the brine shrimp lethality test (BSLT) as described by Sahgal *et al*. (2010) with slight modifications. Artificial seawater was prepared by dissolving 38 g of sodium chloride in 1 L of distilled water, followed by filtration to obtain a clear solution. Brine shrimp (*Artemia salina*) eggs were incubated in the prepared seawater for 48 h under constant aeration to allow hatching into nauplii.

The extract was dissolved in dimethyl sulfoxide (DMSO) to obtain a stock solution of 10 mg/mL. Serial dilutions were prepared to achieve final concentrations of 10, 20, 50, 100, 150, 200, 300, 500, 800, and 1000 µg/mL. For the assay, 10 nauplii were transferred into each test tube containing 5 mL of seawater. Subsequently, appropriate volumes of the extract were added to achieve the desired concentrations.

A negative control containing seawater with 50 µL DMSO (without extract) was included, while vincristine sulphate was used as the positive control. All experiments were performed in triplicate. After 24 h of incubation at room temperature, the number of surviving nauplii was counted, and percentage mortality was calculated. The median lethal concentration (LC_{50}) was determined using appropriate statistical analysis.

Acute oral toxicity study

The acute oral toxicity study of *P. angulata* extract was conducted in accordance with OECD Guideline 423 (Acute Oral Toxicity – Acute Toxic Class Method) with slight modifications. Healthy adult Wistar rats (male and female) weighing 180–200 g were used in this study. The animals were acclimatized for 7 days under standard laboratory conditions (temperature 25 ± 2 °C, 12 h light/dark cycle) with free access to standard pellet diet and water ad libitum.

The animals were randomly divided into control and treatment groups (n = 5 per group, including both sexes). The extract was administered orally via gavage at dose levels of 300, 1000, and 2000 mg/kg body weight. The control group received distilled water only. Following administration, the animals were observed continuously for the first 4 h and periodically for 24 h for signs of toxicity, including changes in behavior, locomotor activity, posture, and mortality.

Further observations were conducted daily for 14 days. Body weights were recorded on Day 0 and Day 14. At the end of the study period, all animals were sacrificed, and vital organs (liver and kidneys) were collected for histopathological examination. All experimental procedures were conducted in accordance with institutional animal ethics guidelines and approved by the relevant Animal Care and Use Committee.

Statistical analysis

All experimental data were expressed as mean ± standard deviation (SD) or standard error of the mean (SEM), as appropriate. Statistical analysis was performed using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test for multiple comparisons.

For toxicity studies, comparisons between control and treated groups were analyzed using one-way ANOVA. A value of $p < 0.05$ was considered statistically significant. All statistical analyses were conducted using IBM SPSS Statistics version 29 (IBM Corp., Armonk, NY, USA, 2024).

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RESULTS

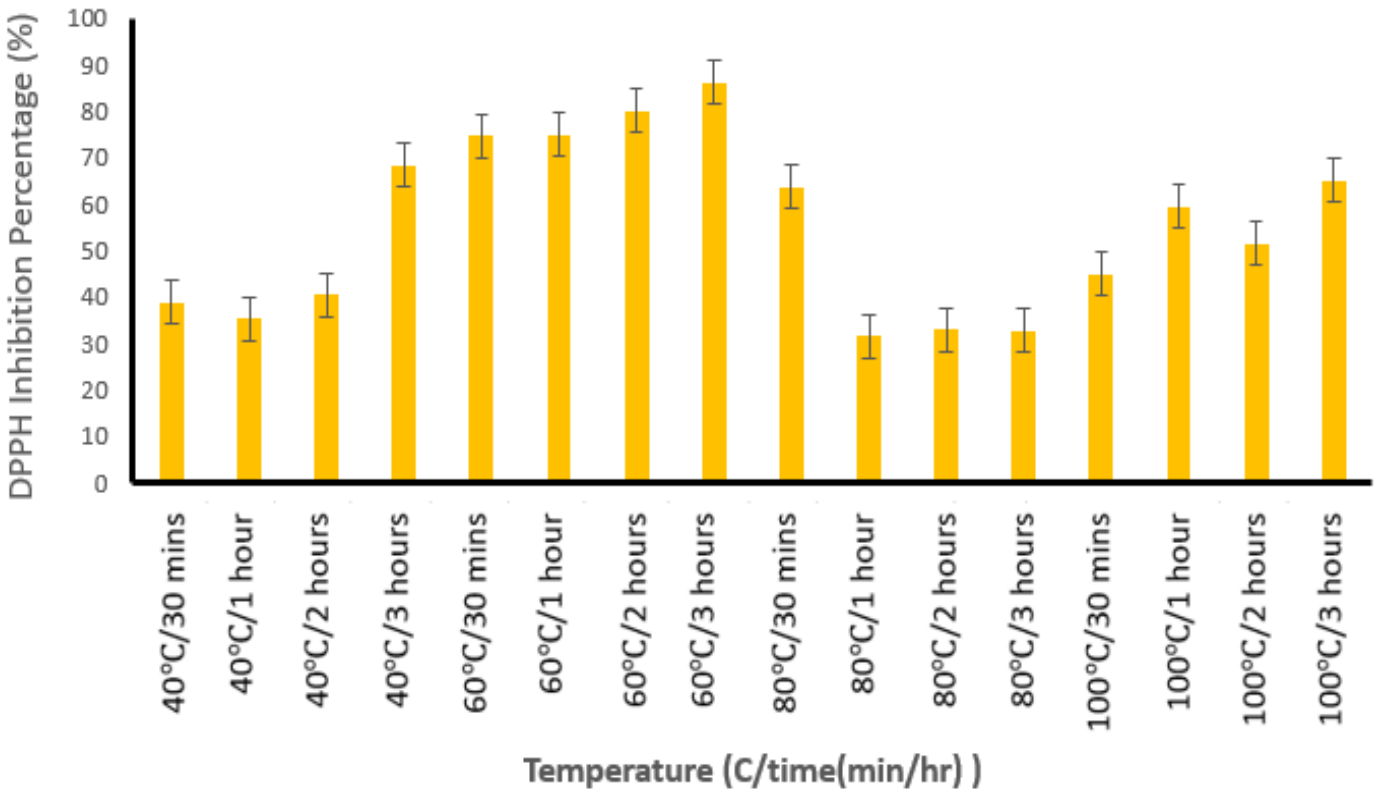

Figure 1: DPPH free radical scavenging activity of *P. angulata* extract with different temperatures and times. Values are mean ± standard deviation (n = 8). Different superscript letters indicate a significant difference at $p < 0.05$.

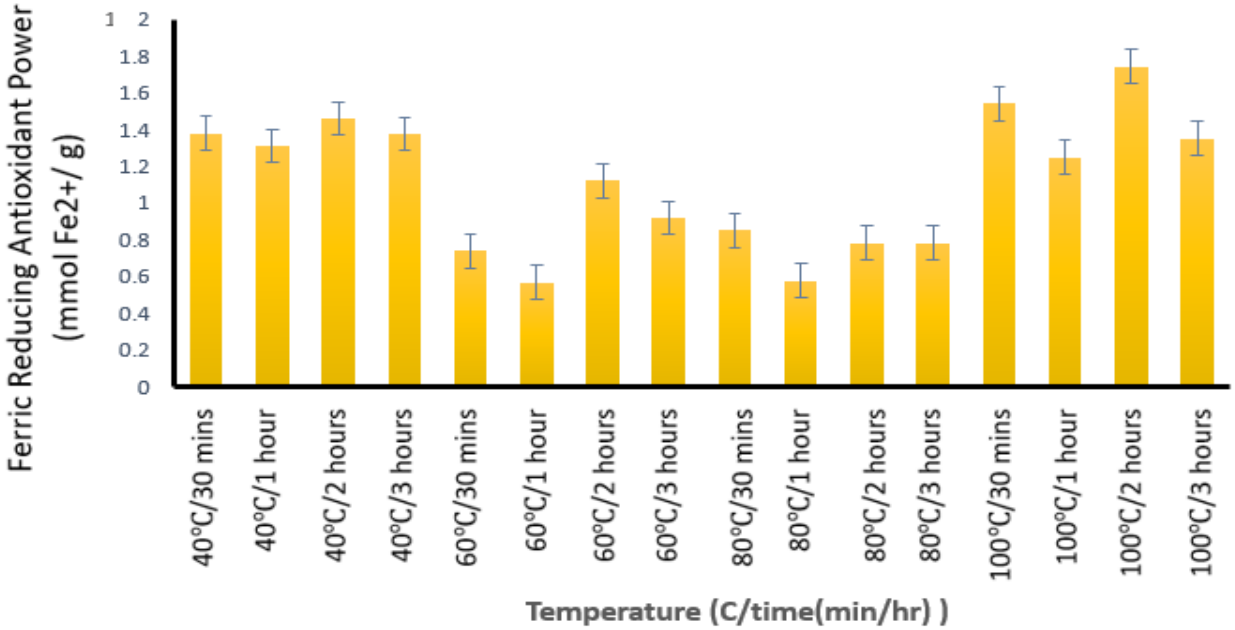

Figure 2: FRAP value of *P. angulata* extract with different temperatures and times. Values are mean ± standard deviation (n = 8). Different superscript letters indicate a significant difference at $p < 0.05$.

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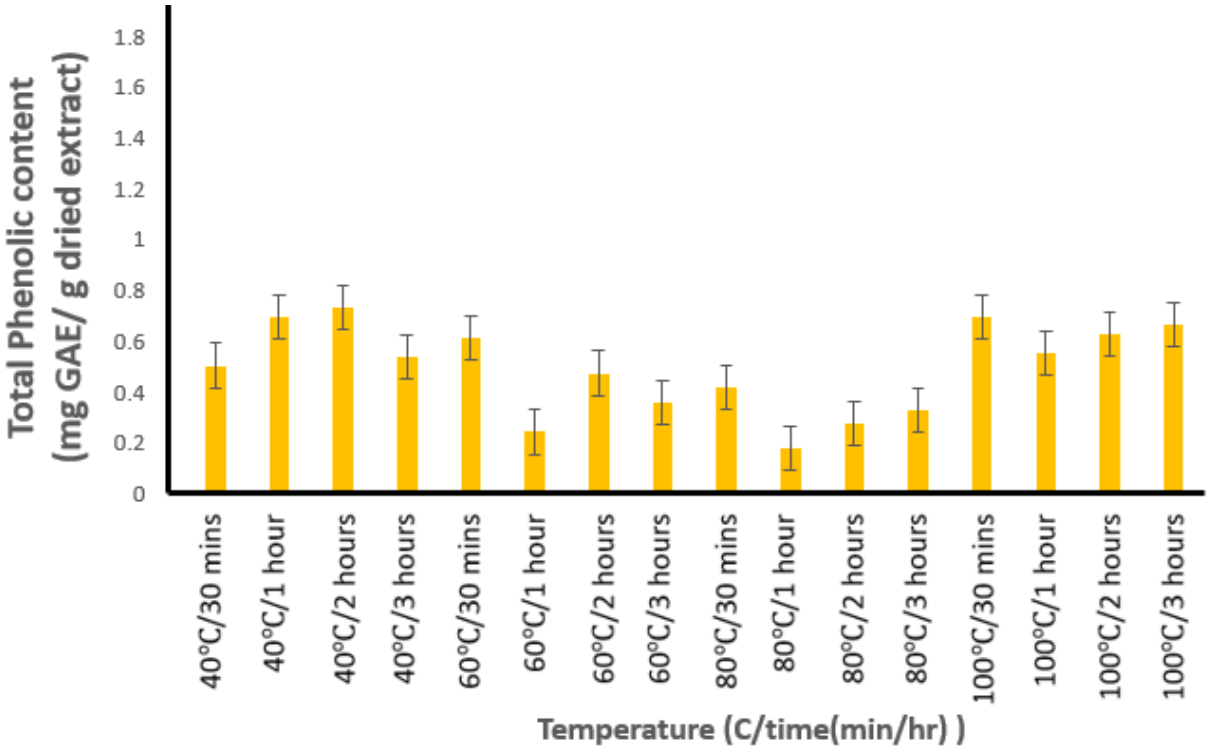

Figure 3: TPC level of *P. angulata* extract with different temperatures and times. Values are mean ± standard deviation (n = 8). Different superscript letters indicate a significant difference at $p < 0.05$.

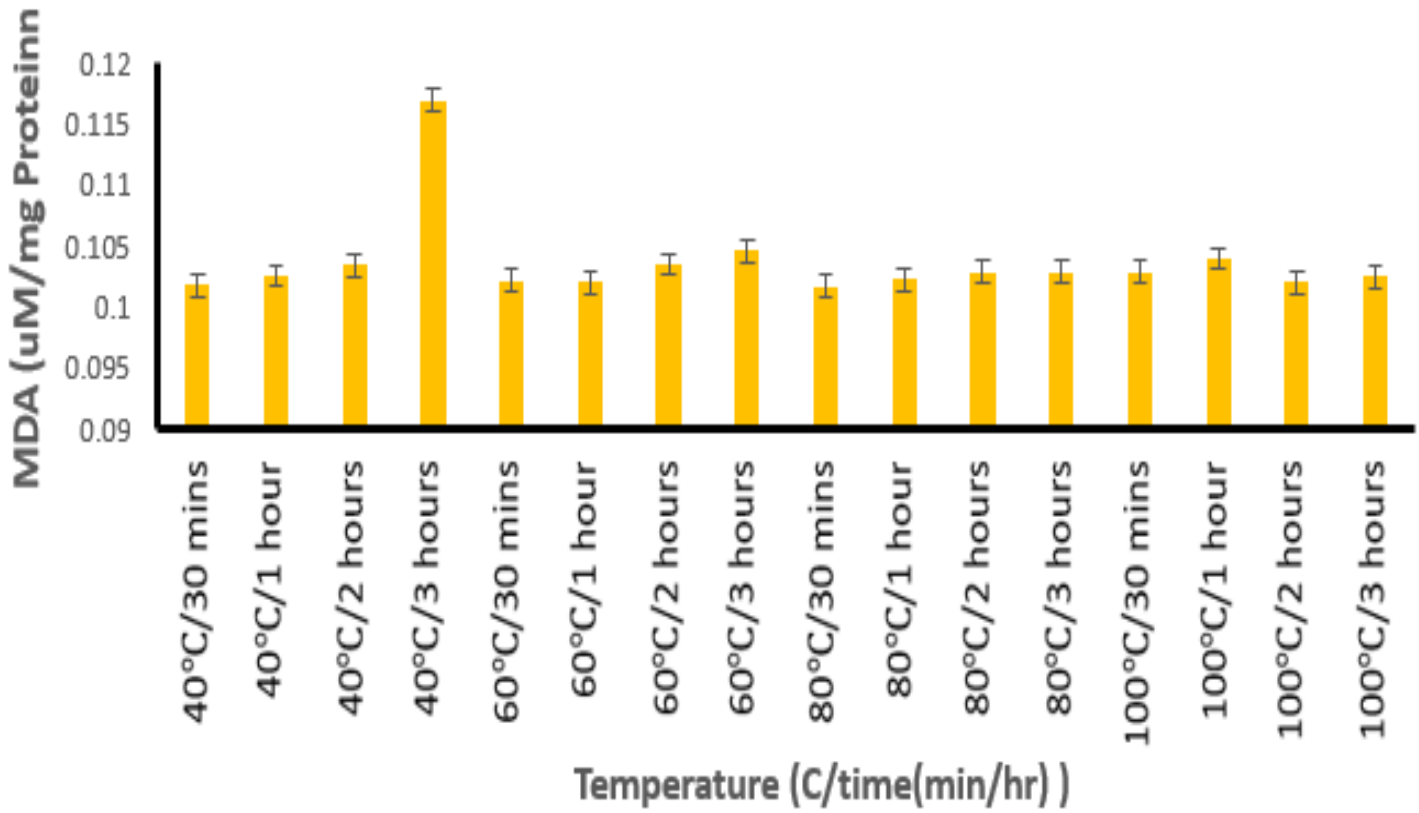

Figure 4: MDA level after treatment of *P. angulata* extract with different temperatures and times. Values are mean ± standard deviation (n = 8). Different superscript letters indicate a significant difference at $p < 0.05$.

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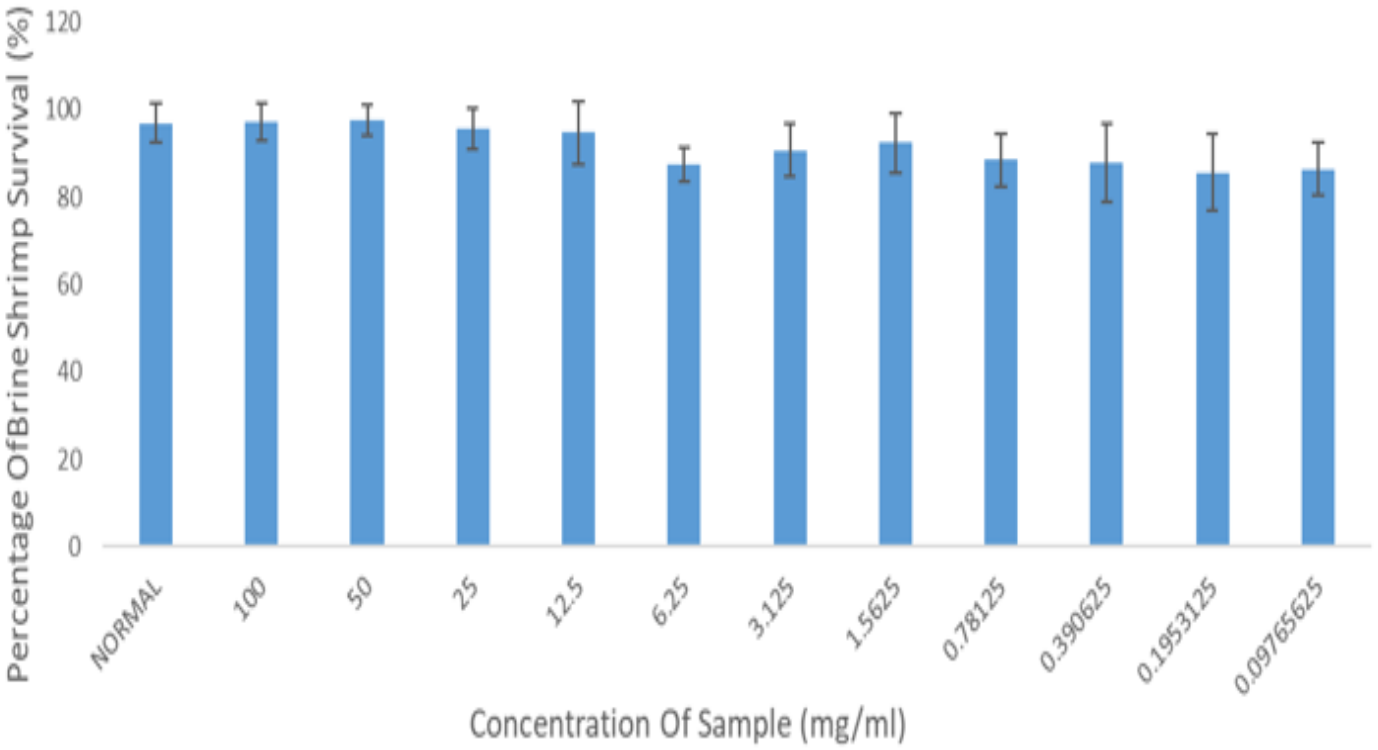

Figure 5: Percentage of Brine shrimp survival against the concentration of *P. angulata.* Values are mean ± standard deviation (n = 8). Different superscript letters indicate a significant difference at $p < 0.05$.

Table 1. Quantitative determination of chlorogenic acid and rutin in *P. angulata* water extract using HPLC analysis. Chlorogenic acid and rutin contents are expressed as concentration (ppm) and percentage of compound in the extract (w/w). Chlorogenic acid and rutin were detected at retention times of 6.8 and 9.5 min, respectively. Values represent individual measurements and mean ± relative standard deviation (RSD).

Sample	Avg. Chlorogenic Acid Conc. ± RSD (ppm)	Avg. % Chlorogenic Acid ± RSD (w/w)	Avg. Rutin Conc. ± RSD (ppm)	Avg. % Rutin ± RSD (w/w)
Water extract of *P. angulata*	103.14 ± 7.94	0.52 ± 7.94	24.31 ± 7.60	0.12 ± 7.60

Table 2. Comparison of rat body weights at the beginning (Day 0) and end (Day 14) of the acute toxicity assessment after treatment with *P. angulata* water extract. No abnormal weight loss was observed during the study period.

Bodyweight of Day 0

RAT	WEIGHT (GRAM)
1	282.7g
2	245.7g
3	256.3g
4	228.2g
5	267.5g

Bodyweight of Day 14

RAT	WEIGHT (GRAM)
1	518.6g
2	497.2g
3	503.1g
4	482.6g
5	512.9g

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Table 3. Behavioral observations of rats following acute oral administration of *P. angulata* water extract. Transient behavioral changes, including mild hypoactivity, brief body shaking, and short periods of sleep, were observed within the first few hours post-administration. No mortality or persistent adverse effects were recorded, and all animals returned to normal activity during the subsequent observation period.

No. of day	Time	Notes
1	15 min	Start the treatment for rat 1 for first time
	30 min	Body shaking, active
	1 hour	Active
	2 hours	Sleep
	3 hours	Active
	4 hours	Active
2	15 min	Start the treatment for rat 1 for second time
	30 min	Stay at one place and running
	1 hour	Sleep
	2 hours	Active
	3 hours	Sleep
	4 hours	Active
3	4 hours	Active
4	4 hours	Active
5	4 hours	Active and normal
6	4 hours	Active and normal
7	4 hours	Active and normal
8	4 hours	Active and normal
9	4 hours	Active and normal
10	4 hours	Active and normal
11	4 hours	Active and normal
12	4 hours	Active and normal
13	4 hours	Active and normal
14	4 hours	Active and normal

DISCUSSION

The present study provides a systematic evaluation of the antioxidant efficacy and preliminary safety of *P. angulata* water extract through optimization of extraction parameters, phytochemical characterization, and toxicological screening. The findings demonstrate that both extraction temperature and duration significantly influence the antioxidant profile and safety characteristics of the extract.

Among the tested conditions, extraction at 80 °C for 30 min produced the highest DPPH radical scavenging activity and total phenolic content, indicating optimal recovery of phenolic constituents under moderate thermal conditions. This observation is consistent with previous studies reporting that controlled heating enhances the release of phenolic compounds by disrupting plant cell walls, while excessive thermal exposure may lead to degradation of thermolabile antioxidants (Maghsoudlou *et al*., 2019; Antony & Farid, 2022).

In contrast, the FRAP assay demonstrated maximal reducing power at 60–80 °C for 1 h, suggesting that slightly prolonged extraction favors the enrichment of electron-donating compounds. Since FRAP primarily reflects the reducing capacity of phenolic acids and flavonoids, these findings indicate that different antioxidant classes respond variably to extraction conditions. Such variation highlights the importance of employing multiple antioxidant assays, as different methods capture distinct mechanisms of antioxidant action (Olszewska *et al*., 2012; Kiss *et al*., 2025).

Interestingly, lipid peroxidation inhibition (MDA assay) was most pronounced in extracts prepared at 100 °C for 2 h, suggesting that higher temperatures may enhance the extraction of compounds involved in inhibiting

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oxidative degradation of lipids. However, when considered alongside DPPH, FRAP, and TPC results, prolonged high-temperature extraction appears less favorable for maintaining a balanced antioxidant profile. This reinforces the need for multi-parameter optimization rather than reliance on a single assay endpoint (Félix *et al*., 2020).

Phytochemical analysis using HPLC confirmed chlorogenic acid and rutin as major phenolic constituents of the extract. These compounds are well-documented for their potent antioxidant and cytoprotective activities. Chlorogenic acid exhibits strong radical scavenging, metal-chelating, and lipid peroxidation inhibitory properties, while rutin is known to enhance endogenous antioxidant defense systems and stabilize reactive oxygen species (Nguyen *et al*., 2024). The presence of these compounds provides a mechanistic basis for the observed antioxidant activity and aligns with previous reports on *P. angulata* phytochemistry (Al Dhabi *et al*., 2015).

From a toxicological perspective, the brine shrimp lethality test indicated low toxicity, with significant lethality observed only at relatively high concentrations. This suggests a favorable preliminary safety margin, consistent with the role of BSLT as an initial screening tool for cytotoxicity (Banti & Hadjikakou, 2021).

The acute oral toxicity study in rats further supported the safety profile of the extract. The absence of mortality, significant body weight changes, and persistent behavioral abnormalities over the 14-day observation period indicates low acute toxicity. The transient behavioral changes observed shortly after administration were mild and reversible, suggesting minimal systemic impact. These findings are consistent with previous studies demonstrating the safety of *P. angulata* extracts within comparable dose ranges (Bastos *et al*., 2008). According to OECD guidelines, such outcomes are indicative of a low risk of acute toxicity.

Collectively, the results of this study suggest that *P. angulata* water extract, when prepared under optimized conditions, exhibits significant antioxidant activity with an acceptable preliminary safety profile. The integration of multi-assay antioxidant evaluation, phytochemical characterization, and in vivo toxicity assessment strengthens the reliability of these findings and supports the potential application of the extract as a natural antioxidant ingredient.

Nevertheless, this study represents an early-stage evaluation. Comprehensive toxicological investigations, including subacute, subchronic, chronic, reproductive, and genotoxicity studies, are necessary to fully establish long-term safety. Future studies should also explore bioavailability, pharmacokinetics, and formulation strategies to further support the development of *P. angulata*-based functional or nutraceutical products.

CONCLUSION

This study demonstrated that extraction temperature and duration are critical factors influencing the antioxidant efficacy of *P. angulata* water extract. Among the conditions tested, extraction at 80 °C for 30 min yielded the most balanced antioxidant profile, characterized by high radical scavenging activity and phenolic content, while optimal reducing power was observed at 60–80 °C for 1 h. Phytochemical analysis identified chlorogenic acid and rutin as key phenolic constituents contributing to the observed antioxidant activity. Preliminary toxicological assessments, including brine shrimp lethality and acute oral toxicity in rats, indicated a favorable safety profile, with no mortality, no significant body weight changes, and only transient, reversible behavioral effects. Overall, *P. angulata* water extract can be considered a promising natural antioxidant source with low acute toxicity under the conditions tested. These findings provide a scientific basis for its further development; however, comprehensive long-term toxicity and efficacy studies are required to support its potential application in nutraceutical or functional product formulations.

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