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IN VITRO STUDIES ON THE INHIBITION OF α-AMYLASE AND α-GLUCOSIDASE BY *MARANTODES PUMILUM* AND *RHINACANTHUS NASUTUS* EXTRACTS

Siti Hajar Adam[a, *], Naguib Salleh[b], Nelli Giribabu[b], Anas Ahzaruddin Ahamad Tarmizi[a]

[a] Department of Pre-Clinical, Faculty of Medicine & Defence Health, National Defence University of Malaysia, Sg. Besi Camp, 57000 Kuala Lumpur, Malaysia
[b] Department of Physiology, Faculty of Medicine, Universiti Malaya, Lembah Pantai, 50603, Kuala Lumpur, Malaysia

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ABSTRACT

This study evaluated the α-amylase and α-glucosidase inhibitory activities of *Marantodes pumilum* and *Rhinacanthus nasutus* leaf extracts as potential natural alternatives for managing postprandial hyperglycemia in type 2 diabetes mellitus. Extracts were prepared using solvents of varying polarities (hexane, ethyl acetate, ethanol, methanol, and water) and compared with acarbose. The hexane extract of *M. pumilum* demonstrated the most potent α-amylase inhibition (IC_{50} = 5.88 µg/mL), exceeding acarbose (IC_{50} = 11.10 µg/mL), while ethyl acetate and methanolic extracts showed moderate inhibition (IC_{50} = 15.74 and 16.31 µg/mL, respectively). For *R. nasutus*, ethyl acetate and ethanolic extracts exhibited significant α-amylase inhibition (IC_{50} = 15.64 and 15.75 µg/mL). Notably, only ethyl acetate extracts from both plants displayed α-glucosidase inhibitory activity, albeit milder than acarbose. The differential inhibitory profiles across extracts suggest that medium-polarity compounds, particularly flavonoids and terpenoids, are responsible for these effects. This study provides evidence for the potential of *M. pumilum* and *R. nasutus* extracts, especially ethyl acetate fractions, as natural enzyme inhibitors with therapeutic potential for managing postprandial hyperglycemia, potentially offering reduced gastrointestinal side effects while maintaining glycemic control.

1.0 INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterised by persistent hyperglycaemia resulting from insulin resistance, impaired insulin secretion, or both. It represents one of the most pressing global health challenges of the 21st century. According to the International Diabetes Federation (IDF), the prevalence of diabetes among adults worldwide has reached 10.5% (537 million) in 2021, with projections suggesting an increase to 12.2% (783 million) by 2045 [1]. Type 2 diabetes mellitus (T2DM), accounting for approximately 90% of all cases, is associated with numerous complications including cardiovascular disease, nephropathy, retinopathy, and neuropathy, highlighting the need for effective glycaemic management strategies. Postprandial hyperglycemia (PPHG) plays a pivotal role in the pathogenesis and progression of T2DM and its associated complications [2-3]. Acute glucose fluctuations trigger oxidative stress, inflammation, and endothelial dysfunction, contributing to micro and macrovascular complications [4]. One established therapeutic approach to mitigating PPHG involves inhibiting carbohydrate-digesting enzymes, specifically α-amylase and α-glucosidase, thereby delaying glucose absorption in the gastrointestinal tract [2, 5]. While conventional pharmaceutical inhibitors such as acarbose, voglibose, and

*Corresponding Author | Adam, S. H. | siti.hajar@upnm.edu.my

miglitol are clinically effective, they frequently cause adverse gastrointestinal effects including flatulence, abdominal discomfort, and diarrhoea, which significantly impact patient compliance and quality of life [3, 6].

In recent years, there has been a shift toward exploring natural alternatives with comparable efficacy but fewer side effects. Medicinal plants, with their complex phytochemical profiles, have emerged as promising sources of bioactive compounds with anti-diabetic properties [4, 7]. *Marantodes pumilum* (Blume) Kuntze (formerly *Labisia pumila*), commonly known as Kacip Fatimah, is a medicinal herb traditionally used in Southeast Asian countries, particularly Malaysia, for women's health [8]. Recent investigations have revealed its potential anti-diabetic properties [9], including improved glucose tolerance and insulin-sensitizing effects [10]. Phytochemical analyses have identified various bioactive compounds in *M. pumilum*, including phenolics, flavonoids, and terpenoids, which may contribute to its therapeutic effects [11-12]. Similarly, *Rhinacanthus nasutus* (L.) Kurz, a medicinal plant native to Southeast Asia and widely used in traditional medicine systems, has demonstrated multiple pharmacological activities including anti-inflammatory, antioxidant, and hypoglycemic effects [13-14]. Recent studies have identified bioactive compounds in *R. nasutus*, such as Rhinacanthins, which exhibit potential antidiabetic activity through various mechanisms [15-16]. Despite these promising findings, comprehensive investigations into the enzyme inhibitory potential of these plants against α-amylase and α-glucosidase remain limited. This study aims to evaluate the in vitro antidiabetic potential of *M. pumilum* and *R. nasutus* by screening various crude extracts for their inhibitory activity against α-amylase and α-glucosidase enzymes. By comparing their efficacy with acarbose, a standard clinical enzyme inhibitor, this research seeks to identify promising plant extracts that may serve as natural alternatives for managing postprandial hyperglycemia in diabetes mellitus. Furthermore, by employing different extraction solvents with varying polarities, this study aims to provide insights into the relationship between solvent polarity and enzyme inhibitory activity, potentially facilitating the identification of the bioactive compounds responsible for the observed effects.

2.0 METHODS AND MATERIAL

2.1. Plant Collection

Fresh leaves of *M. pumilum* and *R. nasutus* were obtained from a supplier in Cameron Highland, Pahang, Malaysia. The plants were identified by a taxonomist and deposited at Herbarium, UM with voucher specimen number No. KLU49047 for *M. pumilum* and KLU 49242 for *R. nasutus*. The fresh leaves were washed and cleaned using running tap water and dried using a laboratory dryer within the temperature range (30-40 ºC) for several days until the leaves were fully dried. The dried leaves were then pulverized to crude powder form and ready for the extraction process.

2.2 Plant Extraction

Powdered plant material (50gm) was placed in a conical flask and extracted with organic solvents such as n-hexane, ethyl acetate, methanol, ethanol, and water (1: 4 ratio) in a mechanical shaker with a constant stirring rate at 250rpm. It was left for 48 hours and solids were filtered using Whatman® filter paper No. 1. (Sigma-Aldrich, St. Louis, MO, USA). The organic filtrates were concentrated *in vacuo* in a rotary evaporator at 50°C to minimise phytochemical degradation while the aqueous extracts were lyophilised. The extraction yield was expressed as:

$$\text{Extraction} = \frac{\text{Dry weight of extract (g)} \times 100\%}{\text{Dry weight of } \textit{the} \text{ leaves (g)}} \quad (1)$$

2.3 Inhibitory Activity against α-Alucosidase

The inhibitory activity against α-glucosidase was assessed by referring to the method of Kim et al. (2004) with slight modifications [17]. This method was carried out using commercially purified α-glucosidase from yeast (Saccharomyces cerevisiae). A stock solution of plant extract was prepared by dilution with DMSO to get a concentration of 100µg/mL, and acarbose and DMSO were kept as positive and negative control respectively. Briefly, 10µL of a sample of different concentrations was incubated with 20µL α-glucosidase in 40ul phosphate buffer (0.1 M, pH 6.8) and 20µL distilled water for 10 min at 37°C and the pre-incubation absorbent reading (A 0 min) was measured by a microplate spectrophotometric reader Multiskan MSTM

*Corresponding Author | Adam, S. H. | siti.hajar@upnm.edu.my

(Labsystems, Minneapolis, USA). The hydrolysis reaction was initiated by incubation with 10 µl of substrate: 5 mM, p-nitrophenyl glucopyranoside (pNPG) for 30 min at 37°C. The hydrolysis of the substrate will produce a yellow-colored solution containing p-nitrophenol that is measured by a spectrophotometer at 405nm (A 30 min). The percentage of α-glucosidase inhibition was calculated based on this equation. The line graph of inhibition (%) vs concentration was plotted and IC50 value of dose-response experiment was obtained and the line graph of inhibition (%) vs concentration was plotted and the IC50 value of the dose-response experiment was obtained.

$$\text{Inhibition}(\%) = \frac{(\text{A}^{30\text{min}} - \text{A}^{0\text{min}})\ \text{Control} - (\text{A}^{30\text{min}} - \text{A}^{0\text{min}})\ \text{Sample}}{(\text{A}^{30\text{min}} - \text{A}^{0\text{min}})\ \text{Control}} \times 100\% \quad (2)$$

2.4 Inhibitory Activity against α-Amylase

The inhibitory activity against α-amylase was assessed by referring to the method of Kwon et al. (2008) with slight modification [18]. The basic principle of this method involved incubation of commercially purified α-amylase from porcine pancreas with *R. nasutus* or *M. pumilum* extract before adding a starch solution that acts as a substrate. The hydrolysis of the substrate yielded the reducing sugar-maltose that was able to reduce 3, 5-dinitrosalicylic acid to form 3-amino-5-nitrosalicylic acid which can be measured by a spectrophotometer at 540 nm. The samples and acarbose were firstly prepared and transferred to a 96-well plate. 50 µL of amylase solution was then added together with 40 µL ddH2O and incubated at 25°C for 5 minutes with constant shaking. 100 µL of starch solution was added to each well and incubated again at 25°C for 7 minutes with constant shaking. 100 µL of DNS solution was kept incubated at 85°C for 30 minutes with shaking with a Thermo-Shaker incubator and the absorbance was read at 540nm once the plate cooled down.

$$\text{Inhibition}(\%) = \frac{(\text{A}_{540}\text{Control} - \text{Blank}) - (\text{A}_{540}\text{Sample} - \text{Blank})}{\text{A}_{540}\text{Control} - \text{Blank}} \times 100\% \quad (3)$$

2.5 Statistical Analysis

All data were analyzed using SPSS Statistics (IBM, New York, USA) and GraphPad Prism (GraphPad Software, California, USA) and are expressed as mean ± standard deviation (SD) from triplicate determinations. IC_{50} values were calculated using nonlinear regression analysis (log[inhibitor] vs. response) in GraphPad Prism. Statistical comparisons between extracts and the positive control (acarbose) were performed using an independent unpaired Student's *t*-test. A probability value of $P<0.05$ was considered statistically significant.

3.0 RESULTS

3.1 Percentage Yield of *M. pumilum* and *R. nasutus leaves* Extract

Among the different solvents, aqueous extraction yielded the highest percentage for both *M. pumilum* (5.25%) and *R. nasutus* (6.20%), followed by methanol (4.8% and 5.73%, respectively). Ethanol extraction also resulted in relatively high yields, with *M. pumilum* at 4.35% and *R. nasutus* at 4.81%. In contrast, ethyl acetate extraction produced a much lower yield (1.55% for *M. pumilum* and 1.61% for *R. nasutus*), while hexane yielded the least extractable compounds (0.25% and 0.82%, respectively). These results suggest that polar solvents, particularly water and methanol, were more effective in extracting bioactive compounds from both plant species, whereas non-polar solvents like hexane resulted in minimal extraction. This trend aligns with the general solubility properties of plant secondary metabolites, which tend to be more soluble in polar solvents. The percentage yields of the extract obtained shown in Table 1.

Table 1: Percentage yield of *M. pumilum* and *R. nasutus* leaves extract

Extractant	*M. pumilum*	*R. nasutus*
Hexane	0.25	0.82
Ethyl acetate	1.55	1.61
Ethanol	4.35	4.81
Methanol	4.80	5.73
Aqueous	5.25	6.20

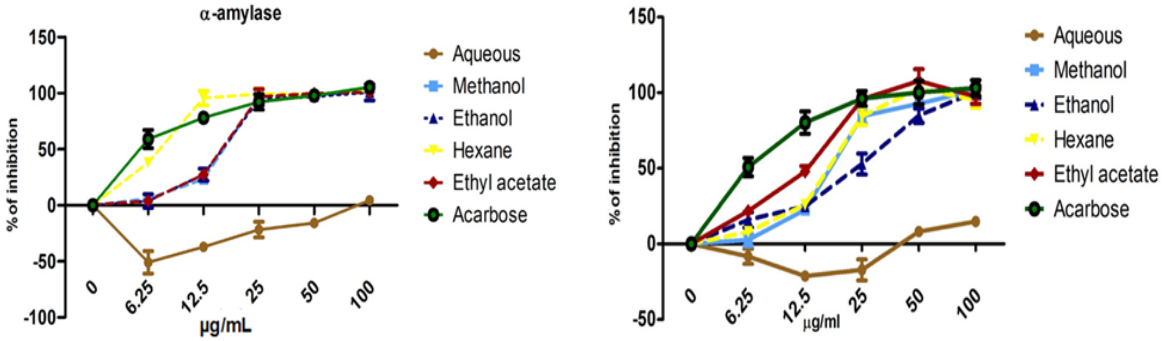
*Corresponding Author | Adam, S. H. | siti.hajar@upnm.edu.my

3.2 α-Amylase Inhibitory Activity of *M. pumilum* and *R. nasutus* Leaves Extract

The α-amylase inhibitory activity of *M. pumilum* and *R. nasutus* leaf extracts (water, methanol, ethanol, hexane, and ethyl acetate) was evaluated using porcine pancreatic α-amylase (Figure 1). At a concentration of 100 µg/mL, *M. pumilum* extracts exhibited inhibition in the following order: hexane (97.5%), ethyl acetate (97.3%), methanol (94%), ethanol (93%), and aqueous (-77%). Similarly, *R. nasutus* extracts followed a comparable pattern, with hexane (96.5%) showing the highest inhibition, followed by ethyl acetate (96%), methanol (95%), ethanol (95%), and aqueous (-86%). Acarbose, the standard inhibitor, displayed 91% inhibition in both methods. In both plant species, the aqueous extract demonstrated the lowest inhibitory activity against porcine pancreatic α-amylase. The IC_{50} values for *M. pumilum* extracts were determined from the corresponding dose-response curves and compared to acarbose (Table 2). Among the extracts, the hexane extract exhibited the lowest IC50 value (5.9 µg/mL), which was even lower than acarbose (11 µg/mL), followed by ethyl acetate, methanol, and ethanol. In contrast, *R. nasutus* extracts showed a slightly different ranking in terms of IC50 values, with the sequence from lowest to highest being acarbose < ethyl acetate < ethanol < hexane < methanol. Overall, both *M. pumilum* and *R. nasutus* demonstrated strong α-amylase inhibitory activity, particularly in their hexane and ethyl acetate extracts, with IC_{50} values comparable to or even lower than acarbose.

3.3 α-Glucosidase Inhibitory Activity of *M. pumilum* and *R. nasutus* Leaves Extract

Ethyl acetate, hexane, methanol, ethanol and aqueous extracts from the leaves of *M. pumilum* were screened for inhibitory activity against yeast (*Saccharomyces cerevisiae*) α-glucosidase. As shown in Figure 2, it was found that only the ethyl acetate extract demonstrated the highest percentage of inhibition (90%) at a dose of 100µg/mL. The methanolic and aqueous extracts yielded the lowest inhibitory activity against yeast (*Saccharomyces cerevisiae*) α-glucosidase enzyme. IC_{50} values of *M. pumilum* ethyl acetate extracts (which showed strong α-glucosidase inhibitory activities during screening) as well as the IC_{50} of acarbose against yeast (*Saccharomyces cerevisiae*) α-glucosidase activity were determined from the corresponding dose-response curves of percentage inhibition versus inhibitor concentration. The IC_{50} for ethyl acetate extract of *M. pumilum* was 68 ± 2.05µg/mL while that for acarbose was 25± 1.32µg/mL Similarly, *R. nasutus* extracts were screened for their inhibitory effects against *S. cerevisiae* α-glucosidase (Figure 4). However, in contrast to *M. pumilum*, *R. nasutus* extracts exhibited minimal inhibitory activity, with only the ethyl acetate extract demonstrating slight inhibition (7.35%) at 100 µg/mL. The inhibitory percentages for the other extracts were as follows: hexane (-20.77%), methanol (-33.68%), ethanol (-17.17%), and aqueous (-25.71%). Due to the low inhibition levels, IC50 values for *R. nasutus* extracts could not be determined. These findings highlight the potential of *M. pumilum* ethyl acetate extract as a promising α-glucosidase inhibitor, whereas *R. nasutus* extracts exhibited negligible activity in this method.



(a) (b)

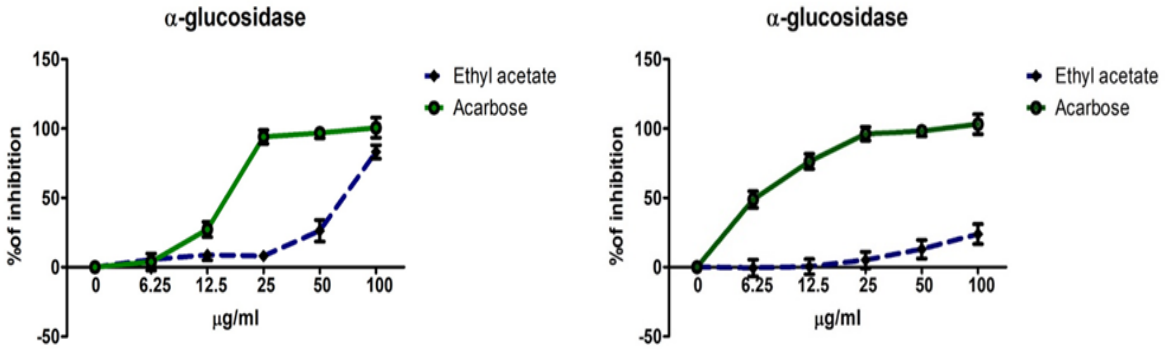
Figure 1. Effects of (a) *M. pumilum* and (b) *R. nasutus* on porcine pancreatic α-amylase activities

Table 2. IC_{50} values of *M. pumilum, R. nasutus* leaves extracts and acarbose against porcine pancreatic α-amylase

Plant extracts	Methanol	Ethanol	Hexane	Ethyl acetate
M. pumilum	16.31 ± 9.67	27.15 ± 7.83*	5.88 ± 2.16*	15.74 ±1.92 *
R. nasutus	80 ± 4.89**	15.75 ± 4.21	49.68 ± 6.37**	15.64 ± 0.82*
Acarbose	11.10 ± 2.05			

*Corresponding Author | Adam, S. H. | siti.hajar@upnm.edu.my

The IC_{50} inhibitory activities of *M. pumilum*, *R. nasutus* leaves extracts and acarbose on porcine pancreatic amylase were determined. Data are presented as mean ± SD values of triplicate determinations; *P<0.05, **P<0.01 significant differences in mean IC_{50} values as determined by unpaired student t-test (versus positive control, Acarbose); IC_{50}: Half maximal inhibitory concentration



(a) (b)

Figure 2: Effects of (a) M. pumilum and (b) R. nasutus on yeast (Saccharomyces cerevisiae) α-glucosidase activity

4.0 DISCUSSIONS

M. pumilum contains various bioactive compounds with different polarities and solubilities. These compounds were extracted using solvents of decreasing polarity (ethyl acetate, hexane, methanol, ethanol, and water) based on Synder's polarity index. This approach effectively isolates different phytochemical classes based on their solubility characteristics. Non-polar solvents like n-hexane extract compounds such as fatty acids, terpenoids, and aglycones [16], while medium-polarity solvents like ethyl acetate and ethanol extract flavonoids, tannins, and terpenoids [10]. Highly polar solvents such as methanol and water extract glycosides, phenolic acids, flavonoids, and alkaloids [8]. Recent phytochemical analyses have identified phenolics, flavonoids, saponins, ascorbic acids, alkenyl compounds, and benzoquinone derivatives in *M. pumilum* leaves [11-12]. These findings provide crucial context for understanding the observed biological activities of different extracts. Our study employed porcine pancreatic α-amylase (PPA), which shares structural and mechanistic similarities with human pancreatic α-amylase [18, 20].

Results showed that ethanolic, methanolic, hexane, and ethyl acetate extracts of *M. pumilum* leaves exhibited inhibitory effects against α-amylase with IC_{50} values of 27.15, 16.31, 5.88, and 15.74 µg/mL, respectively, compared to acarbose (11.10 µg/mL). The hexane extract demonstrated the most potent inhibition, with an IC_{50} lower than acarbose. However, such strong inhibition might not be ideal, as excessive α-amylase inhibition can lead to undigested carbohydrates causing bacterial fermentation in the colon, resulting in gastrointestinal disturbances [2]. The ethyl acetate and methanolic extracts, with IC_{50} values slightly higher than acarbose, represent more suitable α-amylase inhibitors for therapeutic purposes. Recent phytochemical studies have identified flavonoids, isoflavonoids, and phenols in methanolic extracts of *M. pumilum* leaves [8,10]. Among the tested extracts, only the ethyl acetate fraction of *M. pumilum* leaves demonstrated inhibitory activity against α-glucosidase. This suggests that compounds of medium polarity are responsible for this activity. Recent comprehensive reviews have identified flavonoids, tannins, and terpenoids as typical constituents of ethyl acetate extracts [10]. The IC_{50} value for the ethyl acetate extract was higher than that of acarbose, indicating milder inhibition. According to recent analyses [3], compounds with α-glucosidase inhibitory activity typically contain flavonoid structures, terpenes, or phenylpropanoid ring structures. Our findings align with these observations, suggesting that flavonoids present in the ethyl acetate extract are likely responsible for the observed α-glucosidase inhibition.

Interestingly, acarbose showed different affinities between the two enzymes, with lower IC_{50} for α-amylase than for α-glucosidase. This differential binding has been attributed to the large saccharide chain in acarbose having varied binding affinities for these enzymes [19-20]. Various *R. nasutus* extracts were screened for enzyme inhibitory activities. Ethanol, methanol, hexane, and ethyl acetate extracts demonstrated significant α-amylase inhibition, while the aqueous extract showed no inhibitory activity. This observation suggests that α-amylase inhibition is not mediated by highly polar compounds. Among all

*Corresponding Author | Adam, S. H. | siti.hajar@upnm.edu.my

extracts, ethyl acetate and ethanol showed the most potent inhibition of α-amylase with IC_{50} values of 15.64 and 15.75 μg/mL, respectively, compared to acarbose (11.10 μg/mL). This suggests that medium-polarity compounds in *R. nasutus* leaves are responsible for α-amylase inhibition such as flavonoids and glycosides. Regarding α-glucosidase, only the ethyl acetate extract of *R. nasutus* demonstrated mild inhibitory activity. This contrasts with findings by Shah *et al.* [22], who reported significant inhibition by Rhinacanthin-rich extracts obtained through microwave-assisted extraction. These variations suggest that extraction methods significantly influence the yield of active compounds and subsequent enzyme inhibition profiles. Comparing both plants, extracts from *M. pumilum* and *R. nasutus* showed promising α-amylase inhibitory activity, with hexane extracts of *M. pumilum* exhibiting the strongest effect.

For α-glucosidase inhibition, only ethyl acetate extracts from both plants demonstrated activity, albeit milder than acarbose. The differential inhibition patterns observed suggest specific structure-activity relationships that warrant further investigation. Recent molecular studies have identified potential binding mechanisms of plant-derived inhibitors with these enzymes [20]. The mild to moderate inhibition profiles observed, particularly for ethyl acetate extracts, could provide therapeutic advantages over conventional inhibitors like acarbose by reducing gastrointestinal side effects while maintaining glycaemic control.

5.0 CONCLUSIONS

This study demonstrates the significant potential of *M. pumilum* and *R. nasutus* leaf extracts as natural inhibitors of carbohydrate-digesting enzymes for managing postprandial hyperglycemia in type 2 diabetes mellitus. The differential inhibitory profiles observed across various extracts highlight the importance of extraction solvent selection in isolating bioactive compounds with therapeutic potential. Hexane extract of *M. pumilum* exhibited remarkably potent α-amylase inhibition, while ethyl acetate extracts from both plants showed promising dual inhibition of both α-amylase and α-glucosidase enzymes. These findings align with recent phytochemical studies identifying flavonoids, terpenoids, and phenolic compounds in these plants, which likely contribute to the observed enzyme inhibitory activities. The moderate inhibitory profiles of ethyl acetate extracts suggest potential therapeutic advantages over conventional inhibitors like acarbose, potentially offering effective glycemic control with reduced gastrointestinal side effects. Furthermore, the study highlights the value of traditional medicinal plants as sources of bioactive compounds with anti-diabetic properties. Despite the promising findings, this study has several limitations that should be acknowledged. First, the absence of phytochemical profiling means the specific bioactive compounds responsible for the observed enzyme inhibition remain unidentified. Second, the study was limited to in vitro activity using porcine and yeast enzymes, which may not fully replicate human physiological conditions. Additionally, variations in extraction yield and solvent polarity could influence compound availability and activity. Therefore, future studies should include compound isolation and identification, broader in vitro and in vivo models, and mechanism-based assays to better validate the antidiabetic potential of these plant extracts.

Future research should focus on isolating and characterising the specific bioactive compounds responsible for the observed enzyme inhibitory activities, as well as evaluating their efficacy and safety in preclinical and clinical models. Additionally, investigations into the molecular mechanisms underlying these inhibitory effects would provide valuable insights for developing optimized natural formulations for managing postprandial hyperglycemia. This study contributes to the growing body of evidence supporting the integration of traditional medicinal plants into modern therapeutic approaches for diabetes management.

6.0 CONFLICT OF INTEREST

The authors declare no conflicts of interest

6.0 AUTHORS CONTRIBUTION

Adam. S. H. (Methodology; Formal analysis; Data curation; Formal analysis; Investigation; Writing - original draft; Writing - review & editing)
Giribabu, N. (Formal analysis; Writing - review & editing)
Salleh, N. (Project administration; Supervision)
Ahamad Tarmizi, A. A. (editing)

*Corresponding Author | Adam, S. H. | siti.hajar@upnm.edu.my

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*Corresponding Author | Adam, S. H. | siti.hajar@upnm.edu.my