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Original research article

Mango peels and kernels as valuable natural sources of antioxidants and antidiabetics: an *in vitro* study

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ABSTRACT

This study aimed to evaluate through phytochemical profiling the *in vitro* antioxidant activities, α-amylase and α-glucosidase inhibiting activities of the ethanol extracts of the peels and kernels from Thai *Mangifera indica* L. cv. Kiew Morakot, a unique mango cultivar from northern Thailand. Mango peels and kernels were extracted by stirring with 95% ethanol. Concentrations of gallic acid and mangiferin were measured using Ultra high-performance liquid chromatography (UHPLC). The other bioactive constituents were analysed by following standard procedures. The antioxidant activity was determined by DPPH and FRAP assays. The α-amylase and α-glucosidase inhibitory effects were undertaken for antidiabetic activity evaluation. Our results demonstrate that gallic acid is found in both extracts while mangiferin is only found in mango kernel extract. A moderate amount of tannins is found in the mango peel extract, while a significant amount of terpenoids is found in the mango kernel extract. Both extracts of mango exhibited potent antioxidant activity in the FRAP assay (IC_{50} = 886.2±4.16 µM/g of mango peel crude extract and 1,392.8±2.21 µM/g of mango kernel crude extract, respectively). In addition, they displayed a higher α-glucosidase inhibitory potential than acarbose. Conversely, the α-amylase inhibitory effect was slightly lower than for the standard acarbose. The results of this study will form the basis for future work on antioxidants and antidiabetics of mango by-products.

Keywords: mango peels, mango kernels, *Mangifera indica* L., antioxidants, antidiabetics

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https://li01.tci-thaijo.org/index.php/JBAP

1. Introduction

Mango (*Mangifera indica* L.) is an important tropical fruit crop belonging to the family of Anacardiaceae, which consists of numerous species.[1] They are commercially important fruits in tropical areas of Asia, Africa, and Central America. In 2020, the global mango shipments continued to account for approximately 90 percent, in line with a generally assumed attractive taste and high health benefit of these fruits.[2] Mango processing results in large amounts of waste material such as peels and kernels which many studies have shown to contain significant amounts of phytochemical compounds such as mangiferin, gallic acids, and other bioactive compounds.[3-6] These compounds enable the control of diabetes by inhibiting α-amylase and α-glucosidase activities.[3-5]

Both enzymes, α-amylase and α-glucosidase, play an essential role in delaying the digestion of carbohydrates to glucose and reducing the rate of glucose absorption from the small intestine into the bloodstream, reducing serum glucose levels. Earlier studies have indicated that α-amylase and α-glucosidase inhibitors from nature are also potential candidates for developing lead compounds for treating diabetes.[7-8]

Numerous studies have shown comparable α-amylase and α-glucosidase inhibitory effectiveness of the ethanol extract of mango peels from global industries with IC_{50} of 4.0 and 3.5 μg/ml[3] and mangoes from Mexico with IC_{50} of 0.089 mg/ml and 0.080 mg/ml.[9] In the study of mango seeds and kernels, Nigerian *Mangifera indica* L. seed methanol extract displayed inhibition of both enzymes, with IC_{50} values of 710 μg/ml and 340 μg/ml.[10] The ethyl acetate fraction from Chinese mango kernels has so far been found to have the highest antioxidant and α-glucosidase inhibitory capacity, with IC_{50} values of 15.8 and 53.3 μg/ml, respectively.[11] In addition, Thai *Mangifera indica* L. cv. Kaew and Chok Anan seeds have shown a slightly lower α-glucosidase inhibition activity, with IC_{50} of 163.2±2.33 and 113.5±5.86 μg/ml, respectively.[12] Therefore, mango peels and kernels are considered to be a valuable source of nutraceutical ingredients for 537 million adults (20-79 years) living with diabetes worldwide.[13]

In this context, the current study has undertaken the *in vitro* screening of antioxidant activities and α-amylase and α-glucosidase inhibiting activities of the ethanol extracts from the Thai *Mangifera indica* L. cv. Kiew Morakot peels and kernels unique to northern Thailand. There is no scientific evidence of their inhibitory effects on carbohydrate hydrolyzing enzymes. To our knowledge, by-products of mango are currently not considered as industrial waste. Instead, they are turned into a valuable raw material for food ingredients and plant-based natural remedies. The recovery and utilization of mango by-products is an important challenge for food and phytomedicine scientists.

2. Materials and Methods

2.1 Plant Material

Mangifera indica L. cv. Kiew Morakot is a unique mango cultivar originating from the north of Thailand. Its fruits were collected from July to August 2020. The plant material was botanically identified by the Botanical Garden Organization, Ministry of Natural Resources and Environment. Herbarium number is QBG No.128334.

2.2 Extraction procedure

Dried and powdered mango peels (150 g) and mango kernels (4.51 kg) were extracted by stirring with 95% ethanol (1 g/5 ml) for 30 min by maceration at room temperature for 24 h and then filtered through a paper membrane (Whatman No.1 filter paper). Re-extraction with fresh solvent was performed 3 times before a total crude extract was concentrated using a rotary evaporator under reduced pressure at 46 ˚C. The resulting extracts were weighed in vials and stored at −20 ˚C prior to phytochemical analysis. The yield of mango peel and kernel crude extracts were 17.19% w/w (150 g) and 8.67% w/w (4.51 kg), respectively.

2.3 Gallic acid and mangiferin identification

Concentrations of gallic acid and mangiferin were measured using a Dionex Ultimate 3000 ultrahigh pressure liquid chromatography (UHPLC) system with a Diode Array Detector (DAD) (Thermo Fisher Scientific, U.S.A.) at wavelength 254 nm. The column was a Hypersil BDS C-18 (100 x 4.6 mm ID, 3µm). The injection volume was 20 µL. Gradient elution was performed using (A) 0.5% acetic acid with water and (B) methanol. The gradient elution program for gallic acid was as follows: 0 to 8 min with 100% solvent A and then holding until 25 min with 65% solvent A and 35% solvent B. The gradient elution program for mangiferin was as follows: 0 to 9 min 75% solvent A and 25% solvent B, 10 to 19 min 100% solvent B, and then holding until 20 min with 75% solvent A and 25% solvent B. The flow rate was 1 mL/min and the total chromatographic analysis times were 25 min and 20 min, respectively. The peak identification retention times of gallic acid and mangiferin were 3.9 min and 5.9 min, respectively. The data were determined as averages ± SD for triplicates.

2.4 Bioactive constituents identification

Terpenoids, flavonoids, tannins, saponins, and alkaloids were analyzed according to published methods, with slightly modifications.[14] Appearance and disappearance of coloration revealed the presence or absence of such potential groups. Total phenolic content was determined by the Folin-Ciocalteu method.[15] Total phenolics were determined as gallic acid equivalents (GAE) in mg/g of crude extract. The data are presented as averages ± SD for triplicates.

2.5 Determination of antioxidant activity

2.5.1 2,2-Diphenyl-1-picrylhydrazyl radical scavenging ability assay (DPPH)

The antioxidant activity of the mango peel and kernel extracts against DPPH was determined using the method proposed by Thomas et al.[15] with some modifications. Six different concentrations of crude extract were prepared (50, 100, 200, 400, 800, and 1000 µg/mL). Aliquots of 50 µL of each sample were added to 100 µL DPPH (200 µM). The mixture was kept in the dark at room temperature for 30 min. Finally, the free radical scavenging activity of each fraction was determined by comparing its absorbance with that of a blank solution at 517 nm in a UV/VIS spectrophotometer T80 (Oasis Scientific Inc., U.S.A.). The ability to scavenge the DPPH radical was expressed as percentage inhibition and calculated. The results are expressed in milligram equivalents of L-ascorbic acid per milligram of dry weight. The data are presented as averages ± SD for triplicates.

2.5.2 Ferric reducing antioxidant power assay (FRAP)

The ability to reduce ferric ions with mango peel and kernel extracts were determined as described by Sharma et al.,[16] with some modifications. Aliquots of 30 µL of each crude extract with a concentration of 1000 µg/mL were mixed with 270 µL of FRAP reagent. This reagent was prepared by mixing 300 mM sodium acetate buffer pH 3.6, 10 mM tripyridyl-s-triazine (TPTZ) solution, and 20 mM $FeCl_3$ hexahydrate solution (10:1:1). The mixture was incubated for 30 minutes in the dark. Finally, the absorbance was measured at 593 nm in a UV/VIS spectrophotometer T80 (Oasis Scientific Inc., U.S.A.). The reduction of ferric ions of the sample was calculated from a linear calibration curve and expressed as micromolar (µM) $FeSO_4$ equivalents per milligram (mg) of sample. The data are presented as averages ± SD for triplicates.

2.6 Determination of antidiabetic activity

2.6.1 α-Amylase inhibitory activity

The α- amylase inhibitory effect of mango peel and kernel extracts was determined using the method proposed by Keerthana et al.,[17] with some modifications. The crude extracts of mango peels and kernels were dissolved in 10% dimethyl sulfoxide (DMSO) at concentrations of 0.001, 0.01, 0.1, 1, and 10 mg/ml. Acarbose (Sigma-Aldrich, Germany) was used as a standard, dissolved in phosphate buffer to concentrations of

0.00025, 0.0025, 0.025, 0.25, and 2.5 mg/ml. Briefly, a mixture of 600 μ L porcine pancreatic α-amylase (Fluka, Germany), 300 µL 3,5- dinitrosalicylic acid (DNSA) solution, and 0.5% w/v starch (Sigma, Germany) as substrate in 20 mM phosphate buffer, pH 6.7, was incubated at 37 °C for 15 minutes. 2 mL of DNS colour reagent was added, vortexed and boiled in a water bath at 100°C for 10 minutes. The inhibitory activities were measured at an absorbance value of 540 nm using a UV/VIS spectrophotometer T80 (Oasis Scientific Inc., U.S.A.).

2.6.2 α-Glucosidase inhibitory activity

The α-glucosidase inhibitory activities of mango peel extract and kernel extract were determined using the method proposed by Alam et al.,[18] with slightly modification. The crude extracts were dissolved in 10% dimethyl sulfoxide (DMSO) to a concentration of 0.001, 0.01, 0.1, 1, and 10 mg/mL. Acarbose (Sigma-Aldrich, Germany) was used as a standard and dissolved in phosphate buffer to concentrations of 0.0005, 0.005, 0.05, 0.5, and 5 mg/mL. Each reaction contained 10 µL prepared stock solutions, 1 mg α-glucosidase enzyme (Sigma, Germany) in 13.9 mL 50 mM phosphate buffer (pH 6.5), 3 mg p-nitrophenyl beta-D-glucopyranoside (Sigma, Switzerland) in 10 mL of a 50 mM phosphate buffer (pH 6.5) as a substrate and, as reaction stopper, glycine solution (15 g in 100 mL of cold water, pH 10). Each reaction was incubated at 26.8 °C for 15 min. The inhibitory activities were measured at an absorbance value of 415 nm using a Varioskan Flash Multi Detection Microplate Reader (Thermo Electron Corporation, Vantaa, Finland)

2.7 Cytotoxic activity test

Normal cell lines (hTERT-HME1) were purchased from ATCC®. The cells were subcultured in Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 10% fetal bovine serum, 100 units/ml of penicillin, 100 µg/ml of streptomycin, and incubated in a 5% CO_2 incubator at 37 °C. When a cell line reached about 80% confluence, trypsinization was performed, cells were counted and their viability tested with trypan blue using a hemocytometer. A known number of cells (1.5×10^4 cells/well in 100 µL of medium) were seeded into 96-well plate wells for carrying out the MTT method according to Mossman, with modification.[19] 2% Triton-X100 was used as the positive control. Viable active cells reduced yellow MTT salt to insoluble purple formazan, which was dissolved using DMSO. The absorbance of the colored solution was measured at a wavelength of 570 nm using a Varioskan Flash Multi Detection Microplate Reader (Thermo Electron Corporation, Vantaa, Finland). All samples were assayed in triplicate, and the mean for each experiment was calculated.

2.8 Statistical analysis

Results are expressed as means ± S.E.M. of triplets. One way analysis of variance (ANOVA) with Turkey's test or Kruskal-Wallis H test with pairwise comparison was used according to the normal distribution of data; *p values* below 0.05 were considered significant.

3. Results

3.1 Gallic acid and mangiferin

The mango peels and mango kernels are the most promising sources of polyphenols. Table 1 shows the identified bioactive compounds that have been reported to prevent the uptake of carbohydrates and control blood glucose levels. The results show that gallic acid is found in both extracts while mangiferin is only found in mango kernels. UHPLC chromatograms of gallic acid and mangiferin are shown in Fig 1.

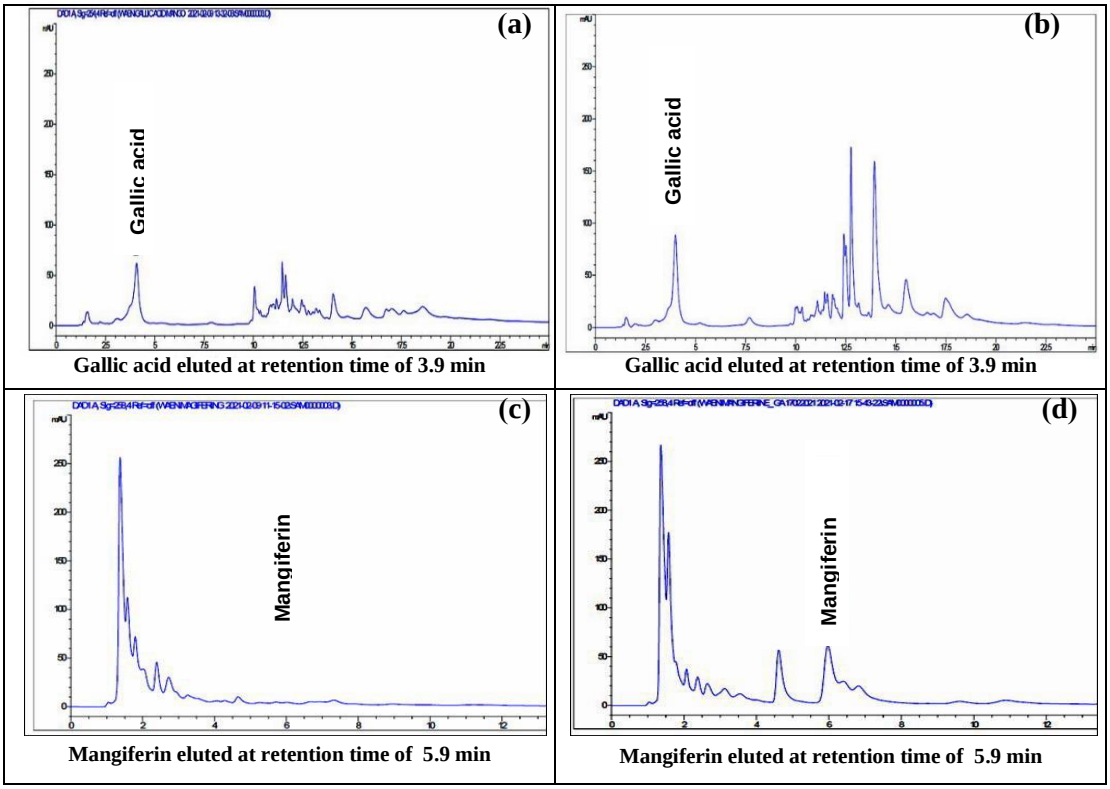

Fig. 1. (a) Chromatogram of gallic acid content in the mango peels. (b) Chromatogram of gallic acid content in the mango kernels. (c) Chromatogram of mangiferin content in the mango peels. (d) Chromatogram of mangiferin acid content in the mango kernels.

Table 1. Phytochemical screening of ethanolic extracts of mango peels and kernels

	Gallic acid (% w/w)	Mangiferin (% w/w)	Terpenoids	Flavonoids	Tannins	Saponins	Alkaloids	Total Phenolic Content Mean±SD (mg GAE/g crude extract)
Mango peels	0.35 ± 0.01	ND	+	ND	++	+	+	76.43±1.14
Mango kernels	0.45 ± 0.01	0.14 ± 0.01	+++	+	+	ND	ND	1114.22±8.36

+: present in small amounts, ++: present in moderate amounts, +++: present in large amounts, and ND: not detected

3.2 Bioactive constituents

Polyphenols (terpenoids, flavonoids, tannins, saponins, and alkaloids) are the most abundant dietary antioxidants of mango fruits and were also investigated. We found that the mango peel extract presented an appreciable moderate amount of tannins, whereas terpenoid, saponin, and alkaloid contents were almost negligible, and flavonoids were not detected. In addition, the mango kernel extract contained a high amount of terpenoids, whereas the flavonoid and tannin contents were almost negligible. Saponins and alkaloids were not detected in mango kernel extract. The phenolic content in the mango kernels extract (114.2±8.36 mg GAE/g crude extract) was higher than that of peel extract (76.4±1.14 mg GAE/g crude extract) (Table 1).

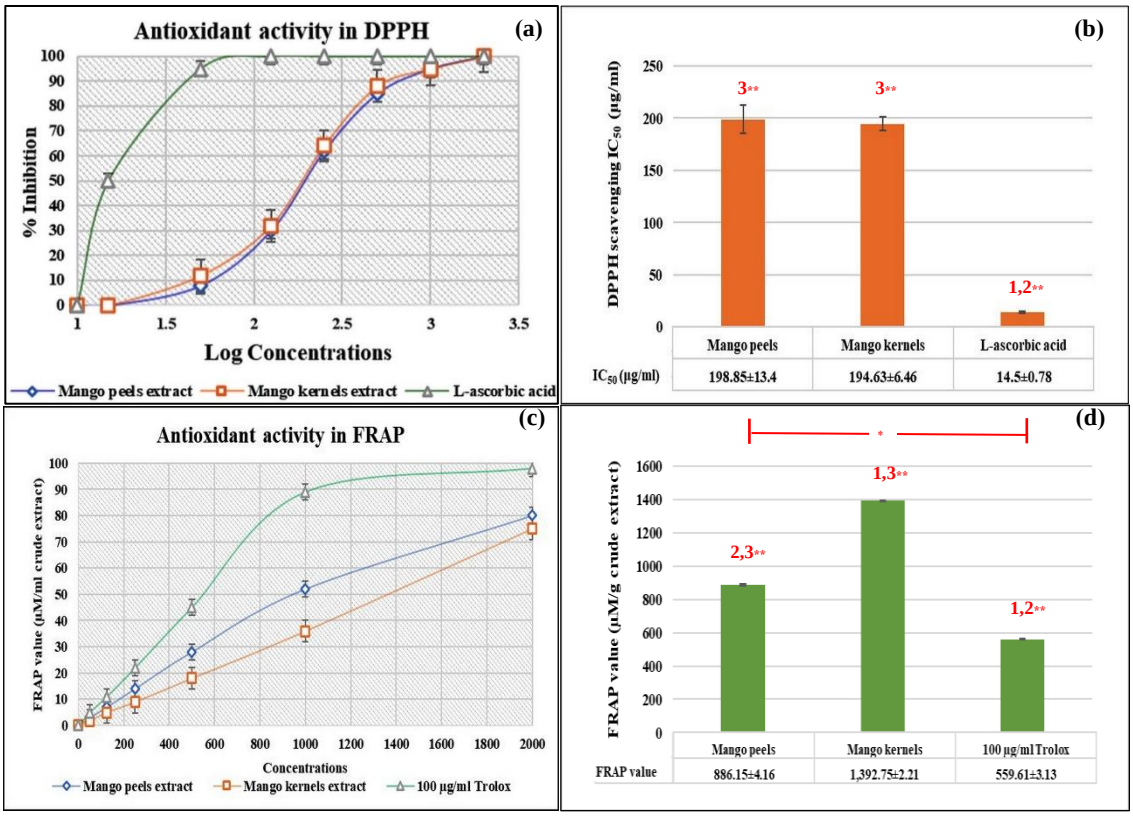

Fig.2. Concentration-response curves and IC_{50}. (a) Concentration-response curves of DPPH assays. (b) DPPH scavenging IC_{50}. (c) Concentration-response curves of FRAP assays. (d) FRAP values. * One Way- ANOVA ($p < 0.001$); ** Post Hoc with Turkey HSD ($p < 0.05$). 1 = mango peels, 2 = mango kernels, and 3 = positive control.

3.3 Antioxidant activity

Fig. 2. displays the percentage antioxidant activity of ethanolic extracts of mango peel and kernel using the DPPH and FRAP assays. Both extracts exhibited lower antioxidant activity ($IC_{50} = 198.9 \pm 13.40$ µg/mL and 194.6±6.46 µg/mL, respectively) compared to L-ascorbic acid ($IC_{50} = 14.5 \pm 0.78$ µg/mL) in the DPPH assay. The difference in antioxidant activity between both mango extracts and L-ascorbic acid was significant ($p < 0.05$). However, the Fe^{3+}- TPTZ reducing power of both extracts (IC_{50} = 886.2±4.16 µM/g of mango peels crude extract and 1,392.8±2.21 µM/g of mango kernels crude extract, respectively) was comparable to that of Trolox (IC_{50} = 559.6± 3.13 µM/g of crude extract) in the FRAP assay ($p < 0.001$). Significant differences were found in all pairwise comparisons between groups for the FRAP assay ($p < 0.05$).

3.4 Antidiabetic activity

Fig. 3. presents a screening of α-amylase and α-glucosidase enzyme inhibitory activity. Mango peel extract and mango kernel extract respectively exhibited 43.9 and 19.7-fold stronger inhibition of the α-glucosidase enzyme when compared to the standard acarbose. Conversely, the α-amylase inhibitory effect of both extracts was lower than for the standard acarbose ($p < 0.05$). Thus, a significant difference between both mango extracts and acarbose inhibition of α-glucosidase enzyme activity was found for all pairwise comparisons ($p < 0.05$). The same was true for α-amylase inhibition ($p < 0.05$).

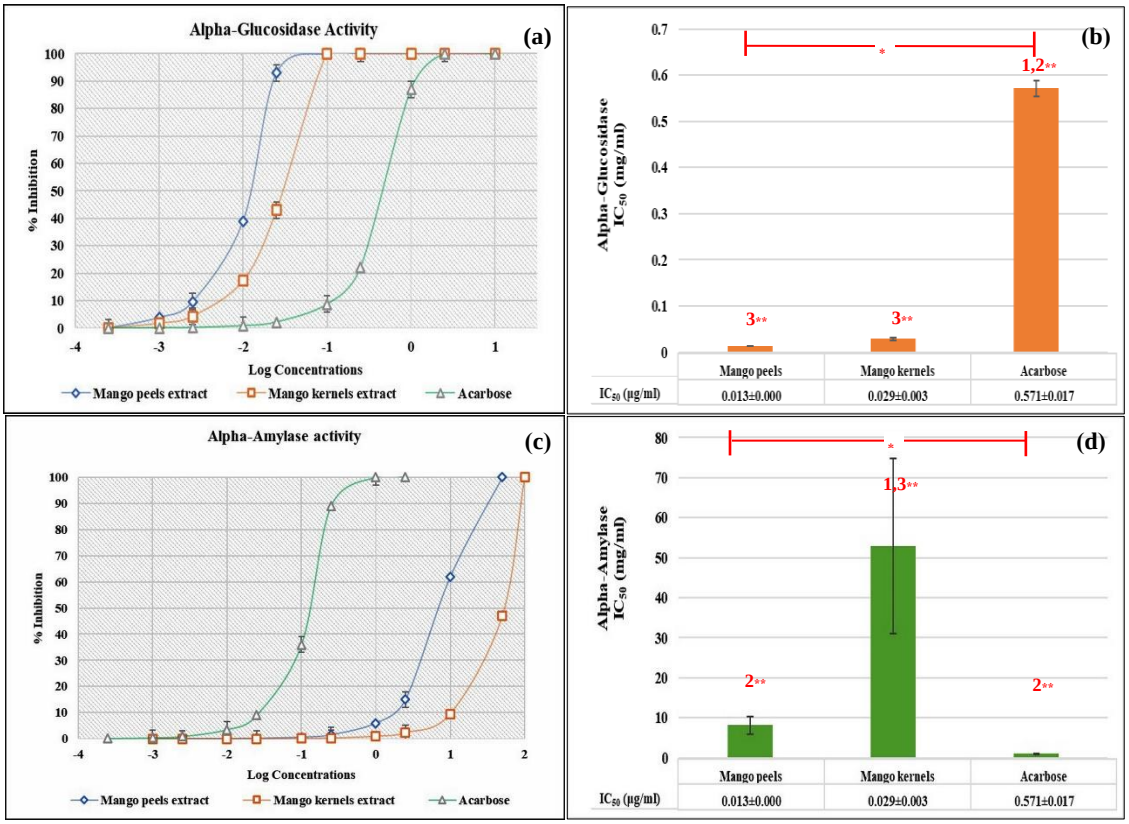

Fig. 3. Concentration-response curves and IC_{50}. (a) Concentration-response curves of α-glucosidase inhibition. (b) α-glucosidase activity IC_{50} values. (c) Concentration-response curves of α-amylase inhibition. (d) α-amylase activity IC_{50} values. * Kruskal-Wallis H test ($p < 0.05$); ** Pairwise comparison ($p < 0.05$). 1 = mango peels, 2 = mango kernels, and 3 = positive control.

Table 2. Cytotoxic activity of ethanolic extracts of mango peels and kernels against hTERT-HME1 human normal cells

	IC_{50} (µg/ml)			
	Mango peels extract		Mango kernels extract	
	24 h	48 h	24 h	48 h
hTERT-HME1	>1,000	>1,000	>1,000	>1,000

3.5 Cytotoxic activity test

Table 2 presents half maximal inhibitory concentrations of cytotoxic activity of mango peel extract and mango kernel extract for 24 h and 48 h. We conclude that neither mango peel extract nor mango kernel extract has a cytotoxic effect on normal cells with IC_{50} values of more than 1,000 µg/ml.

4. Discussion

This study shows that gallic acid is found in ethanolic *Mangifera indica* L. cv. Kiew Morakot mango peel and kernel extracts, whereas mangiferin is only found in the kernel extract. This is in contrast to published mangiferin levels in the peels of eleven Chinese mango cultivars which ranged from 0. 04 to 7. 49 mg/ g DW. [20] Similarly, Mexican mango cultivars have

reported mangiferin levels of 157 to 1259 µg/ g DW in three Ataulfo mango peel extracts.[21,22] Interestingly, Ecuadorian Tommy Atkins mango cultivar peel extracts showed a large mangiferin concentration of 411 mg/100 g DW, although no mangiferin was observed in Keitt cultivar mango peel.[23] Spanish mango cultivars also contain higher mangiferin levels in the kernels (22.5–72.8 mg/100 g DW) than in the peels (4.1–29.8 mg/100 g DW).[24] This indicates that mangiferin is differentially dispersed in parts of mango. Free phenolics are found in storage tissue such as endosperm and often in dead or dying tissues.[25] Therefore, it is not surprising that mango kernels are an important source of gallic acid and mangiferin.

One other type of polyphenols contained in mango peel extract were tannins. Flavonoids were not detected. The mango kernel extract contained a high amount of terpenoids, but saponins and alkaloids were not detected. This coincides with a study of Ahmed et al.[26] that revealed large amounts of terpenoids and tannins in mango kernel extract. In addition, Nakpanich et al.[27] did not detect saponins and alkaloids in raw mango seed kernel extracts. The present findings indicate a higher amount of phenolics in mango kernel extract than in mango peel extract. Although similar concentrations have been reported in previous studies[26,28,29] (98.7± 8.8 mg/g, 112 mg/g, and 117±13.5 mg/g, respectively, in kernel extract), Nakpanich et al.[27] reported a higher total phenolic compound concentration of 411.8 mg of GAE/g of raw mango kernel extract. In contrast, the peel and kernel extracts in the present study showed higher phenolic content than reported by Pinsirodom *et al*.[30] who found total phenolic compound concentrations between 9.86-19.66 meg GAE/g fresh WT and between 38.88-66.95 meg GAE/g fresh WT, respectively, in peel and seed kernels of green mature Thai mangoes of six cultivars (Khiew Sawoey, Nam Dokmai, Rad, Chok Anan, Fah Lan, and Kaew Dum). The appearance of these features can be explained by the degradation of phenolic compounds. They are dependent on the temperature of the extraction method and extracting solvent which affect phytochemicals.[31-32] In addition, Ajila, Bhat and Rao[33] revealed that dietary fiber content and phytochemical content were higher in ripe peels than in raw peels.

Our results show an inversion behavior for DPPH and FRAP assays with both extracts, a finding which agrees with previous reports by Verónica et al.[23] and López- Cobo et al.[24] Their results exhibited strong scavenging activity in the FRAP assay but low antioxidant potential according to the DPPH assay. This finding was also similar to an earlier study by Pinsirodom et al.[30] who reported that mango seed kernels from two out of six Thai cultivars had the highest FRAP activities of 61 and 72 mg Trolox®/g fresh WT. They also reported that the ferric-reducing capacity was found in mango kernels rather than in mango peels.[23,24] The empirical evidence from this study indicates that the difference between DPPH and FRAP assays could be attributed to total phenolic content. Previous studies have shown a strong positive correlation between total phenolic content and FRAP assay activity,[34-35] which is consistent with the results of this study. Different mechanisms of action could also affect antioxidant activity. The high hydrogen-donating potential of crude extract results in good DPPH activity, while a high degree of ferric ion (Fe^{3+})-ligand complex reduction to ferrous (Fe^{2+})-ligand complex results in high FRAP activity.[36,37] In addition, the different potencies of crude extracts compared to the standards of DPPH and FRAP assays might be influenced by the presence of multiple bioactive compounds in the crude extract. Multiple bioactive compounds may lead to synergistic or antagonistic effects.[38] Moreover, the extraction process or subsequent storage conditions of the crude extracts might impact the yield and/ or stability of bioactive compounds.

Of particular note, mango peel extract potentially inhibited α- amylase and

α- glucosidase activity more than mango kernel extract. This finding is in agreement with the report of Gondi and Rao[3] who revealed the inhibition of these key enzymes by the ethanol extract of mango peel. Additionally, α- glucosidase inhibition was stronger than α- amylase inhibition. This finding is also consistent with that reported by Gondi and Rao,[3] as well as Irondi et al. [10] In contrast to our findings, ethanolic *Mangifera odorata* L. seed kernel extract displayed higher α- amylase and α-glucosidase inhibitory activity compared to peel extract. The inhibitory activity against α-amylase was also more potent than against α-glucosidase. [39] The inhibition of α-amylase and/or α-glucosidase is an effective treatment of diabetes mellitus type 2. Although acarbose is an oral α- glucosidase and α- amylase inhibitor drug, its use is associated with side effects due to excessive pancreatic α-amylase inhibition, leading to the accumulation of undigested carbohydrates in the colon and serving as substrate for bacterial fermentation. Prolonged use of acarbose can result in severe gastrointestinal complications such as flatulence, diarrhea, and abdominal distention. [40] As suggested by previous studies, mild α-amylase inhibition activity is desirable. [41] A more potent α- glucosidase inhibitor may have higher specificity for its target enzyme, meaning it selectively inhibits the intended biological pathway without affecting other enzymes or processes. Thus, stronger inhibition of α-glucosidase compared to acarbose needs to be investigated for the potential advantage of fewer clinical side effects in.

Finally, our cytotoxic activity tests showed no effect on normal cells by either extract, a finding comparable to previously published research that concluded mango peels and mango kernels can be used as natural plant- based medicines with fewer side effects than acarbose or other synthetic drugs.[3,10,39]

5. Conclusion

Our results highlight that both seed and peel extracts of *Mangifera indica L.* cv. Kiew Morakot show promise as antioxidants. The stronger inhibition of α-glucosidase and lesser inhibition of α-amylase, compared to acarbose, may indicate higher specificity and selectivity and potentially fewer clinical side effects than acarbose. This preliminary study suggests that mango by-products are a valuable natural source of antioxidants and antidiabetic agents. Further exploration of the health benefits of mango by-products through *in vitro* and *in vivo* studies is essential.

Acknowledgements

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Conflicts of Interest

The authors declare no conflict of interest.

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