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Original article

Phenolic content of Thai Bao mango peel and its *in-vitro* antioxidant, anti-cholinesterase, and antidiabetic activities

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A R T I C L E I N F O

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A B S T R A C T

Plant phenolics have been known for various biological activities. This study aims to extract and examine the presence of phenolics in Bao mango (Mangifera indica L. var.) peel ethanolic extract (MPE). Further, antioxidant, anti-diabetic (α-amylase, and α-glucosidase inhibitory activity), and anti- Alzheimer's disease (AD) (acetylcholinesterase (AChE), butyrylcholinesterase (BChE), and β-secretase (BACE-1) inhibitory activity) efficacy of MPE were determined. The results indicated that mangiferin (8755.89 mg/ 100 g extract) was the major phenolic compound in MPE. An antioxidant mechanism revealed that MPE had a higher radical scavenging ability (4266.70 μmol TE/g extract) compared to reducing power (FRAP) or oxygen radical absorption capacity (ORAC). Further *in-vitro* enzyme inhibitory assay against diabetic and AD involved enzymes showed that MPE had stronger inhibitory action against an enzyme involved in diabetes compared to their standard drug (Acarbose) ($P < 0.05$). While a lower IC_{50} value was observed against AD-involved enzymes compared to their standard drug (donepezil) ($P < 0.05$). The results show that Thai Bao mango peel byproduct can be a potential source of nutraceuticals to lower diabetes and improve cognitive health.

1. Introduction

Fruit consumption provides considerable health benefits owing to a higher amount of phytoactive compounds. In Thailand, the estimated agricultural production in 2023 was 46.87 billion USD, compared to 43.665 billion USD in 2022 (ITA, 2024). With the increasing agricultural production, the waste and by-products from fresh produce industries were also increased. These wastes or byproducts (peel, seed, must, and other products) accounted for 10–60 % of the fresh produce (Koirala et al., 2024). The majority of these wastes are merely disposed of in municipal landfills, which pollute the environment and pose health risks. Significant dietary and financial losses as well as environmental issues, for instance, leachate contamination and greenhouse gas emissions, have resulted from this (Esparza et al., 2020). With increasing demand and proportional production, the waste from fruit processing industries will rise in tandem with an increase in agricultural production. The recovery of added-value compounds, such as phytochemicals, from fruit and vegetable waste provides an opportunity to minimize environmental hazards and economic losses for the country. The majority of the phytochemicals found in fruit waste include flavonoids, polyphenols, tannins, carotenoids, isothiocyanates, isoflavones, lignans, saponins, and so on (Nirmal et al., 2023). Several reports have been published on different phenolic compounds obtained from fruits and vegetable byproducts that can prevent or reduce the severity of a wide range of diseases including inflammatory, diabetic, heart disease, tumor, hypertension, and hyperlipidemia (Nirmal et al., 2015; Rajput et al., 2022).

Mangos are widely consumed around the globe due to its distinct taste. The mango peel accounts for 10–12 % of the total fruit, making it a significant byproduct of the mango industry (Tacias-Pascacio et al., 2022). Fruit peels are being reintroduced in the agro-food industry as valuable byproducts because of their large content of polyphenols,

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phytosterols, carotenoids, and vitamins, which possess health improvement ability (Jahurul et al., 2015; Marçal & Pintado, 2021). Mango peels contain a majority of phytochemicals that exhibit various activities including inhibition of oxidation, bacteria, and inflammation, reduce blood glucose and cholesterol levels, etc. (Abbasi et al., 2017; Gondi et al., 2015; Luo et al., 2021). For example, mango cv. '*Ataulfo*' peel contains mangiferin, quercetin, and catechins, which are known for anti-diabetic activities by improving impaired insulin resistance (Gondi et al., 2015; Preciado-Saldaña et al., 2022; Zahid et al., 2022). Especially, mangiferin (a xanthone) is the most prevalent and potent antioxidant compound found in mango (Zafra Ciprián et al., 2023) and exhibits anti-Alzheimer action. Mangiferin was reported to interact with neural components, prevent the synthesis of Aβ, inhibit mitochondrial dysfunction, downregulate stress pathways, and eventually counteract neuroinflammation (Sarkar et al., 2020).

In our previous study, we assessed the potential antioxidative and anti-bacterial activities of Bao mango peel. The mango peel waste extracts showed excellent antioxidant and antimicrobial activities due to phytochemicals such as mangiferin and other polyphenols (Gondi et al., 2015; Koirala et al., 2024). This study aimed to determine the *in-vitro* anti-diabetic and anti-AD properties of Bao mango peel extract powder. The *in-vitro* analyses were conducted using enzyme inhibitory assays. AChE, BChE, and BACE-1 enzymes were used for the anti-AD activity, while α-amylase, and α-glucosidase, were used for anti-diabetic assay. Additionally, the major phytochemical in MPE was identified using chromatography coupled with mass spectrometry.

2. Material and methods

2.1. Mango peel collection and extraction process

The Thai Bao mango peels were obtained from Promsap Thailand Company Limited, Hat Yai, Songkla, Thailand. Upon arrival, samples were washed and cleaned under running tap water to remove any external debris. Later on, dried at 50 °C in a hot air oven to achieve a moisture content of less than 10 %. After drying, the peels were ground to powder.

The dry powder 5 g was added to 250 ml of 80 % ethanol and macerated at 40 °C for 2 h. The filtrate obtained upon filtration was concentrated at 40 °C using a rotary evaporator. The concentrated solvent was lyophilized for subsequent analyses.

2.2. Total phenolic content (TPC) and identification of phenolic in MPE

The TPC of the MPE was determined using the Folin-Ciocalteu (FC) method as discussed by Sripum et al. (2017). The phytochemicals in MPE powder were identified and quantified using the liquid chromatography-electrospray ionization tandem mass spectrometry (LC-ESI-MS/MS) as suggested by Sirichai et al. (2022). All standards used during analysis were HPLC grade with > 98 % purity (Sigma-Aldrich, St. Louis, MO, USA). Mangiferin was analyzed using [M + H] ion mass with a parent ion of 423.100 *m/z*. Selectivity and specificity of mangiferin in the sample were analyzed using 3 SRM transitions at specific radio frequencies (RF-lens; 108 V) and collision energies (V), which were 273.054 *m/z* (23.58 V), 303.113 *m/z* (17.76 V), and 327.071 *m/z* (16.88 V). The calibration curve of mangiferin was performed in triplicates using concentrations ranging from 0.125-10 μg/mL and a retention time of 1.116 min. A linear plot of mangiferin was presented as indicated in Equation (1):

$$y = ax \pm c \tag{1}$$

where *x* is a mangiferin concentration, *y* is the ion peak area, a is a linear slope (7516.2) and c is a constant (195.48). The correlation coefficients (R^2; 0.9985), limit of detection (LOD; 0.04 μg/mL), and limit of quantification (LOQ; 0.13 μg/mL) were calculated from Equations (2) and (3)

$$LOD = (3.3\sigma)/S \tag{2}$$

$$LOQ = (10\sigma)/S \tag{3}$$

where S: average slope and σ: standard deviation.

For establishing accuracy, known amounts of the mangiferin standard were added at three different concentrations (low level = 102.20 μg/mL, medium level = 91.14 μg/mL, high level = 91.57 μg/mL) into the sample solution. The solutions were injected into the system and the mangiferin content in spiked samples was determined using Equation (4), where the method's accuracy was expressed as percentage recovery (%):

$$\%\,\text{recovery} = [(\text{detected amount} - \text{initial amount}) \times 100]/\text{injected amount} \tag{4}$$

2.3. Antioxidant assays

The antioxidant potential of MPE was investigated in various forms such as reducing power, radical scavenging ability, and oxygen radical absorbance capacity as mentioned by Sripum et al. (2017).

2.4. Enzyme inhibition assay

The enzyme inhibitory assays were performed as explained by Suttisansanee et al. (2019) and indicated in Table 1. Acarbose and donepezil were used as a standard drug for diabetes and AD, respectively. The inhibition potential was calculated and expressed as a percentage inhibition using Equation (5):

$$\%\,\text{inhibition} = \left(1 - \frac{B-b}{A-a}\right) \times 100 \tag{5}$$

where *A* and *B* are the absorbance of a reaction with an enzyme (without MPE) and an enzyme with MPE, respectively. Similarly, *a* and *b* are the absorbance of the control blank and sample blank, respectively.

The enzymes bought from Sigma-Aldrich are AChE (*Electrophorus electricus,* 1000 units/mg); BChE (equine serum ≥ 10 units/mg); α-amylase (porcine pancreatic, type VII, ≥10 unit/mg); α-glucosidase (*Saccharomyces cerevisiae*, type I, ≥10 U/mg protein); BACE-1 FRET assay kit.

2.5. Statistical determination

All experiments and analyses were performed in triplicate and presented as mean ± SD with a *p*-value less than 0.05 considered significantly different. SPSS software was used to analyze statistical differences

Table 1
Enzyme inhibitory assay parameters.

Enzymes Concentration and volume	Substrate Concentration and volume	Indicator	MPE	Absorbance (nm)
Enzymes associated with Alzheimer's disease				
AChE (0.25 μg/mL) 100 μL	ACh (0.32 mM) 50 μL	DTNB (16 mM)		
BChE (1.5 μg/mL) 100 μL	BCh (0.4 mM) 50 μL	10 μL	40 μL	412
BACE-1	BACE-1 FRET assay kit			λ_{ex} = 320 nm λ_{em} = 405 nm
Enzymes associated with diabetes				
α-Amylase (0.6 mg/mL) 100 μL	pCNM (1 mM) 50 μL		50 μL	405
α-Glucosidase (0.2 U/mL) 10 μL	pNPG (10 mM) 25 μL + KPB (pH 7), 160 μL		5 μL	

among different samples and assays.

3. Results

3.1. TPC and phenolic content of MPE

The TPC in the MPE was calculated to be 512.62 mg GAE/g MPE powder (Table 2). The presence of phenolic compounds in MPE was determined with LC-ESI-MS/MS. The phenolic profile (Table 2) indicated that among 25 authentic phenolic standards, mango peel extract consisted of predominant mangiferin, which was significantly higher than 3,4-dihydroxybenzoic acid by 45.1-fold, while a trace of naringenin was detected. The chromatogram of the extract shows three major peaks in addition to other minor peaks (Fig. 1).

3.2. Antioxidant activities

The DPPH radical scavenging assay, FRAP, and ORAC were noted to be 4266.70 ± 313.36, 1765.90 ± 170.17, and 1405.59 ± 108.18 μmol TE/g MPE powder, respectively (Table 3). The superior antioxidant activity was detected in the DPPH radical scavenging assay, which was 2.4- and 3.0-fold higher than those detected in FRAP and ORAC potential, respectively.

3.3. Enzyme inhibition assays

The inhibitory effect of MPE powder against α-amylase, α-glucosidase, AChE, BChE, and BACE-1 is shown in Table 4. Regarding the inhibitory potential of MPE against type II diabetes enzymes, an IC_{50} of 3.46 μg/mL was found in MPE against α-amylase, While an IC_{50} of 0.19 μg/mL against α-glucosidase was noted. In the case of AD-involved enzymes, MPE exhibited the IC_{50} of 3.09 and 27.50 μg/mL against the AChE and BChE, respectively. While MPE showed 43.51 ± 0.92 % inhibition against BACE-1 with a 25 μg/mL concentration of extract; thus, its IC_{50} was more than 25 μg/mL.

4. Discussion

4.1. Phenolic content of MPE

Several studies examined the TPC content in the mango peel obtained from different mango cultivars. Marcillo-Parra et al. (2021) reported that the MPE from the Haden variety showed the highest TPC of 6624 mg GAE/100 g DW, whereas *Tommy Atkins*-G exhibits the lowest TPC of 2930 mg GAE/100 g DW. According to different research, the TPC of the mango and its byproducts varied significantly as *Mangifera indica L* from different Thai cultivars (9.56 to 21.35 mg GAE/g fresh weight) (Pinsirodom et al., 2018), *Tommy Atkins* mango peel (2032–3185 mg GAE/100 g DW) (Barreto et al., 2008; Sogi et al., 2013) and thai mango *Xiangya* (1376 mg/100 g DW) peel (Abbasi et al., 2015). The phenolic content of fruits widely varies depending upon the variety, environmental conditions, harvest stage, and most importantly the solvent and process of extraction. Mangiferin is the primary bioactive compound in mango peel. Zahid et al. (2022) reported compounds mangiferin 6′-gallate and mangiferin with [(M−H)$^-$] at m/z 573.0886 and m/z 421.0776, respectively. A study carried out by Barreto et al. (2008) identified and quantified the phenolic composition of various Brazilian mangoes by-products, including barks, peels, kernels, and young and old leaves, and reported the presence of magniferin, methyl gallate, and penta-O-galloyl-glucoside in significant amounts. Mangiferin was the major compound in all the by-products and exhibited higher FRAP, DPPH radical scavenging, and ORAC abilities. Likewise, López-Cobo et al. (2017) identified that the MPE of various mangoes (Sensación, Osteen, and Keitt) had a significant amount of phenolics like galloyl glucose, gallic acid, ferulic acid, gallotannins, and protocatechuic acid. Similar research on the phytochemical composition of MPE among different varieties reported a significant proportion of mangiferin (5.72 to 314 mg/100 g DW) in the MPE (Marcillo-Parra et al., 2021). Berardini et al. (2005) examined varying concentrations of mangiferin in different species of mango, such as 126.3 mg/100 g DW in Tommy Atkins, 1.1 mg/100 g DW in Haden, and 1.4 mg/100 g DW in Kent. The phenolic content of the MPE might have been significantly affected by the method of extraction or the region where it is grown (Marcillo-Parra et al., 2021).

Table 2
Phenolics and total phenolic contents of mango peel extract.

Phenolics	Standard ions (*m/z*)	SRM transitions (*m/z*)	RF Lens (V)	Contents
Phenolic profile (mg/100 g MPE powder)				
Mangiferin	423.100	273.054, 303.113, 327.071	108	8755.89 ± 901.81 [a]
3,4-Dihydroxybenzoic acid	152.95	109.113, 81.042, 91.042	128	193.96 ± 8.41[b]
Naringenin	272.938	146.97, 153.054, 119.000	160	5.14 ± 0.35[b]
TPCs (mg GAE/g MPE powder)				512.62 ± 23.70

Results are presented as a mean ± SD of triplicate analyses. Different superscript small letters in the last column indicate significant differences.

4.2. Antioxidant activities

Plant phenolics are known for protecting the body from both internal and external oxidative stress to prevent cell damage (Tacias-Pascacio et al., 2022). The potent antioxidant activities of these compounds are due to their distinctive functional groups and chemical structure. To assess antioxidant potential more thoroughly, several approaches based on the various ways that phenolic compounds can function as antioxidants based on their structural features have been developed (Sarkar et al., 2022). The antioxidant properties of phenolics are derived from the reactive potential of the hydroxyl group on their aromatic ring or the phenol moiety. By donating electrons or hydrogen, phenols can neutralize free radicals (Nirmal et al., 2022). Liu et al. (2017) reported that the FRAP values for the methanolic extract of mango peel from different cultivars ranged between 0.016 and 0.122 mmol $FeSO_4$/g DE, which were lower than those of the present study. Likewise, ORAC values for mango peel were reported to range between 0.42 and 0.78 mmol TE/g DE in the Tommy Atkins variety (Sogi et al., 2013). Ajila et al. (2007) investigated the antioxidant properties of different varieties of Indian mango peel and found that IC_{50} values varied from 1.83 to 4.54 μg/ml of GAE and that antioxidant activity was in the manner of concentration dependent. This difference in the antioxidant properties can be explained by numerous variables, including the genome, sample preparation, extraction methods, and solvent composition, which can influence the phenolic content and various antioxidant levels (Sarkar et al., 2022).

4.3. Anti-diabetic and anti-AD activities

The α-amylase and α-glucosidase enzymes are associated with type II diabetes complications. Hence the inhibition of this enzyme was related to the lowering diabetic complications. The IC_{50} of MPE against α-amylase was 2.7-fold lower than acarbose, a commercial anti-diabetic drug. Additionally, IC_{50} of MPE against α-glucosidase was 1.8-fold lower than acarbose. These data indicated that mango peel extract could pose as an effective anti-α-amylase and anti-α-glucosidase agent with high potential anti-diabetic properties. MPE and mangiferin were used in a recent *in vivo* study to treat alloxan-induced diabetic rats, where a significant decrease in fasting glucose was reported after 21 days of

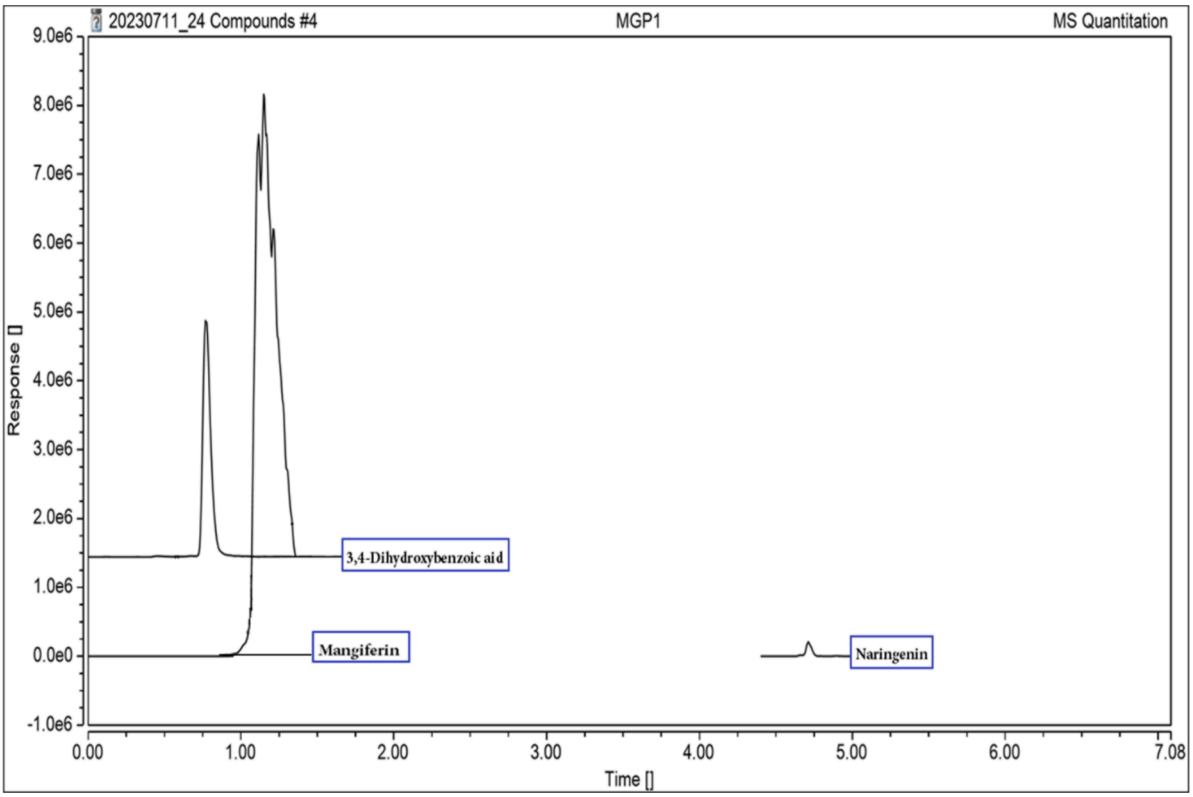

Fig. 1. Chromatogram of MPE.

Table 3
Antioxidant potential of MPE.

Assays	Activity (μmol TE/g MPE powder)
DPPH radical scavenging	4266.70 ± 313.36 [a]
FRAP	1765.90 ± 170.17[b]
ORAC	1405.59 ± 108.18[b]

Results are presented as a mean ± SD of triplicate analyses. Different superscript small letters in the column indicate significant differences.

Table 4
Enzyme inhibitory activities of mango peel extract.

Enzyme	IC_{50} (μg/mL)		
	MPE	Acarbose	Donepezil
α-amylase	3.46 ± 0.40[b]	9.41 [a]	NA
α-glucosidase	0.19 ± 0.02[b]	0.34 [a]	NA
AChE	3.09 ± 0.17 [a]	NA	1.18[b]
BChE	27.50 ± 1.24 [a]	NA	0.81[b]
BACE-1	>25 [a]	NA	0.50[b]

Results are presented as a mean ± SD of triplicate analyses. Different superscript small letters in the row indicate significant differences. NA: not available.

treatment compared to the untreated group (Mistry et al., 2023). It was suggested that the extracts alter the pathway involved in the synthesis of glycogen in diabetes groups by elevating glycogen levels in the liver and muscles (Mistry et al., 2023). Similarly, Gondi et al. (2015) examined the glucose-lowering potential of MP powder in diabetic rats and noted that supplementation of 5 % and 10 % MPP in the diet lowered oxidative stress along with a remarkable reduction in the serum glucose level and other associated parameters. It was evident that α-amylase and α-glucosidase are prone to a wide range of polyphenols, for instance, 3,4-hydroxybenzoic acid (Guan et al., 2022) and mangiferin (Santos et al., 2022), as the unique nature of these phenolic compounds makes them have an affinity to bind with digestive enzymes like α-glucosidase. A significant concentration of these compounds has been detected in the present study, which could have resulted in α-glucosidase and α-amylase inhibition. Oxidative stress is associated with the different pathways of diabetes, such as the glycation end-products pathway, polyol, protein kinase C activation, and hexosamine pathway (Ighodaro, 2018).

The accumulation of amyloid beta peptides gets deposited in the brain as plaques, and the loss of cholinergic neurons leads to AD pathogenesis (Rajput et al., 2020b). Inhibition of cholinesterases (butyrylcholinesterase (BChE) and acetylcholinesterase (AChE)) that degrade neurotransmitters is crucial (Moussa-Pacha et al., 2020; Rajput et al., 2020a). Phytochemicals from mango and its byproducts have been reported to have inhibitory potential for activities against neurotransmitters, acetylcholine, and degrading enzymes, AChE and BchE (Temviriyanukul et al., 2022). However, compared to donepezil, which acts as a competitive cholinesterase inhibitor, the inhibitory potentials of mango peel extract were 2.6–44.0-fold higher, suggesting lower inhibitory strength against these enzymes. A similar result was noted in inhibitory activity against BACE-1, a β-amyloid plaque-producing enzyme. The mango peel extract exhibited much lower inhibitory strength against BACE-1 compared to donepezil with an IC_{50} of 0.5 μg/mL. This inhibitory potential of the MPE could be due to the abundance of mangiferin in the extract. Temviriyanukul et al. (2022) examined the potential AD-associated enzyme inhibition by different varieties of *M. indica* (Namdokmai, Kimju, and Keaw in Thailand) and found that the 0.25 mg/mL concentration showed strong AChE and BChE inhibition (69–83 % and 70–84 %, respectively), among which *M. indica* 'Namdokmai' showed superior inhibition properties against AChE, BACE-1, and BChE. In the same study, anti-AD properties in the *Drosophila* model showed a significant reduction of BACE-1 in the brains of AD flies (6.03 U/mL) by 250 μg/mL of *M. indica* 'Namdokmai' extract (Temviriyanukul et al., 2022). The present results indicated that Bao MPE showed higher inhibitory activity against enzymes involved in AD compared to the above-reported mango variety from Thailand. The long-

term supplementation of mangiferin with a dose of 40 mg/kg to mice with $AlCl_3$-induced AChE activity, indicated that mangiferin inhibits the expression of AChE produced by $AlCl_3$ (Kasbe et al., 2015).

5. Conclusion

Mangiferin was the major phenolic compound in Bao MPE powder followed by 3,4-dihydroxybenzoic acid, while a trace of naringenin was detected. The antioxidant assays indicated that MPE had high potential in scavenging free radicals followed by reducing ability on oxygen radical absorbance capacity. The IC_{50} values of crude phenolic extracts from mango peel against α-amylase and α-glucosidase were significantly lower than those of a commercial inhibitor (Acarbose) indicating the potential application of Bao MPE in diabetic treatment. Similarly, MPE showed inhibitory activity against the enzymes involved in AD (AChE, BChE, and BACE-1). However, MPE was not comparable to the standard drug of AD (donepezil). As a potential source of mangiferin with potent antioxidant, anti-diabetic, and anti-AD properties, the present study sheds light on the utilization of Thai native Bao mango peel byproduct as a nutraceutical and functional food product application.

CRediT authorship contribution statement

Sirinapa Thangsiri: Writing – original draft, Formal analysis, Data curation. **Uthaiwan Suttisansanee:** Writing – original draft, Supervision, Methodology, Investigation. **Pankaj Koirala:** Writing – original draft, Visualization, Formal analysis, Data curation. **Wimonphan Chathiran:** Writing – original draft, Methodology. **Warangkana Srichamnong:** Writing – original draft, Validation, Software. **Li Li:** Writing – review & editing, Validation, Software. **Nilesh Nirmal:** Writing – review & editing, Visualization, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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