International Journal of Agricultural Technology 2024 Vol. 20(2):749-760
Available online http://www.ijat-aatsea.com
ISSN 2630-0192 (Online)

The biological activities of the methanolic extract of santol (*Sandoricum koetjape*) fruits

Poeaim, S.[1] and Pedklang, N.[2*]

[1]Department of Biology, School of Science, King Mongkut's Institute of Technology Ladkrabang (KMITL), Ladkrabang, Bangkok 10520 Thailand; [2]Department of Science and Bioinnovation, Faculty of Liberal Arts and Science, Kasetsart University, Kamphaeng Saen Campus, Nakhon Pathom 73140, Thailand.

Poeaim, S. and Pedklang, N. (2024). The biological activities of the methanolic extract of santol (*Sandoricum koetjape*) fruits. International Journal of Agricultural Technology 20(2):749-760.

Abstract The biological activities of phytochemical, antibacterial, antioxidant, anti-tyrosinase and cytotoxic activities from flesh and peel of santol (*Sandoricum koetjape*) fruit by macerating with methanol were inverstigated. Phytochemical screening in the methanolic extracts revealed the presence of tannin, coumarin and betacyanin. Saponin was found only in the flesh, and alkaloid was found only in the peel extracts. For antibacterial activity, the extract concentration at 2000 micrograms per disc was found to be inhibitory effects on the growth of *Bacillus cereus* and *Staphylococcus aureus* but no inhibitory effect on the growth of *Escherichia coli*. DPPH and ABTS methods for antioxidant activity, the peel extract exhibited higher activity than the flesh extract. The IC_{50} values of methanolic extracts from the peel of santol fruit were 30 and 48 micrograms per milliliter for DPPH and ABTS, respectively. Tyrosinase inhibitory activity was determined by the dopa-chrome method. The peel extract showed higher tyrosinase inhibitory activity than the flesh extract, with 76.37% at 1 milligram per milliliter. For cytotoxicity activity, the flesh and peel of santol extracts at a concentration of 2000 micrograms per milliliter showed the cytotoxic effect on the human colorectal adenocarcinoma cell line (HT-29) and African green monkey kidney cell line (Vero) at 47.39 and 37.18 percent, respectively. This research showed the pharmacological potential of the santol fruit extracts for further testing to develop as products.

Keywords: *Sandoricum koetjape*, Santol, Biological activities

Introduction

Santol (*Sandoricum koetjape* Merr.), a popular seasonal fruit, is widely consumed in Southeast Asia for its unique flavor and various health benefits. This large, fast-growing tree can reach up to 50 meters with a straight trunk. The fruits are yellowish rounded, 4 to 6 cm in diameter and have a thick outer layer. They contain various health benefits due to their nutritional constituents, such as polysaccharides, vitamins, and natural antioxidants. Furthermore, *S. koetjape* has a wide range of traditional medicinal uses; its leaves can relieve fever, its bark and roots can treat diarrhea and stomachaches, and it can be applied to get rid of ringworm. Studies have

[*] **Corresponding Author:** Pedklang, N.; **Email:** naruporn.p@ku.th

reported various phytochemical compounds from santol fruits, seeds, leaves, and bark, including alkaloids, flavonoids, glycosides, saponins, steroids, and tannins. Moreover, these compounds show various medicinal properties, such as antimicrobial effects, inflammation reduction, cytotoxicity, and anti-angiogenic in cancer cells.

The bioactive compounds from *S. koetjape* stem bark extract have demonstrated anti-inflammatory properties in an induced mouse ear inflammation model and induced DNA damage leading to apoptosis in human colon cancer cells (HCT 116) (Nassar *et al*., 2012; Rasadah *et al*., 2004). Triterpene compounds that are isolated from *S. koetjape,* such as ketonic acid, sandorinic acid, sentulic acid, and koetjapic acid, have shown cytotoxic activity in a human myeloid leukemia cell line (HL-60), human breast cancer cell line (MCF-7), and human colon carcinoma cell line (HCT-116) (Wijaya, 2022). *S. koetjape* is rich in tannins, which are polyphenolic natural products with anticancer potential. Tannins exhibit anti-inflammatory, anti-proliferative, and pro-apoptotic effects (Kleszcz *et al*., 2023). Furthermore, *S. koetjape* leaf extract has shown antibacterial activity against *Staphylococcus mutans* (Pambudi *et al*., 2021). This study investigated the extraction of *S. koetjape* flesh and peel on their bioactivity properties such as phytochemical, antibacterial activity, antioxidant activity, tyrosinase inhibitory activity and cytotoxicity.

Materials and methods

Extraction of plant material

Santol fruits were bought at a neighborhood market in Bangkok, Thailand. The flesh and peel were cleaned in water (components shown in Figure 1) and separated and sliced into small pieces. Subsequently, both finely chopped parts were dried at 45°C for three days. The coarsely ground samples were then extracted with methanol at a ratio of 1:5 by weight. The filtration was used filter paper (Whatman No.1) to get filtrate, then evaporated using the vacuum rotary evaporator. The crude methanol extract was kept in an amber glass bottle and stored in a desiccator until completely dried.

Test for phytochemical constituents

The phytochemical screening of methanolic extract was analysed and qualitatively by using different standardized test procedures that were carried out for tannins (Farnsworth, 1966; Evans, 2002), alkaloids (Farnsworth, 1966; Houghton and Raman, 1998), saponins (Farnsworth, 1966; Santos *et al*., 1997), anthocyanin and betacyanin (Farnsworth, 1966; Evans, 2002), and coumarins (lactone glycosides) (Harborne, 1998).

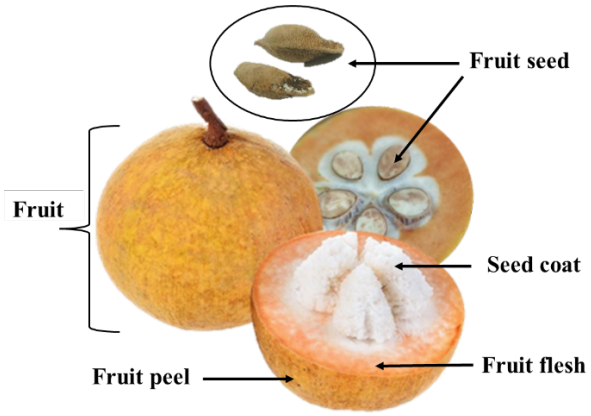

Figure 1. The structure of Santol fruit

Test for antibacterial activity

The antibacterial activity was assessed using the paper disc diffusion method against three bacterial strains, namely *Bacillus cereus* DMST 5040, *Escherichia coli* ATCC 25922 and *Staphylococcus aureus* TISTR 1466, following the protocol of CLSI (2012). Bacteria were cultured and incubated in Mueller-Hinton Broth (MHB) for 18-24 hours. Standardize turbidity using normal saline solution (0.90% NSS) and measured the optical density (OD) to achieve a range of 0.08-0.13 at 625 nm through spectrophotometry. Then, each stain was applied to Mueller Hinton Agar (MHA) using a swab and allowed to air-dry on the surface for 3-5 minutes. The raw extracts were dissolved in methanol and applied onto a 6 mm diameter disc (1000-3000 µg/disc), placed paper disc on MHA and incubated for 16-18 hours. After that, the diameter of the inhibition zone was measured and reported in millimeters (mm). Gentamicin (10 µg/disc) was the positive control, while methanol was the negative control.

Test for antioxidant activity

The antioxidant activity was assessed by measuring the scavenging activities against 2,2-diphenyl-1-picrylhydrazyl (DPPH) and 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) radicals. The DPPH and ABTS assays were conducted following the procedures outlined by Armania *et al*. (2013) and Poeaim *et al*. (2016), with minor adjustments. Various concentrations (10-40 µg/mL) of Trolox were used to construct the standard curve and as the positive control. The calculation was determined the percentage of radical scavenging activity. The 50% inhibition concentration (IC_{50}) values were determined using GraphPad Prism 6.0 software. The findings were presented as the antioxidant capacity in milligrams of Trolox equivalent per gram of extract (mgTE/g extract).

Test for anti-tyrosinase activity

The dopachrome method was investigated anti-tyrosinase activity according to Natungnuy *et al*. (2018) with few modifications. The dopachrome method, as outlined by Natungnuy *et al*. (2018) with minor modifications, was conducted to examine anti-tyrosinase activity. The study was partitioned into four groups. Control group A comprised a mixture of 80 µL of phosphate buffer (pH 6.8) and 20 µL of tyrosinase enzyme (25 U/mL). In contrast, the blank of control (B) lacked the tyrosinase enzyme and the sample. Group C, designated as the sample group, included a combination of phosphate buffer, tyrosinase enzyme, L-DOPA, and 60 µL of the sample, with concentrations of 500 and 1000 µg/mL. The blank of sample group (D) did not contain tyrosinase enzyme. The 40 microliters of 2.5 mM L-Dopachrome (L-DOPA) were introduced into 96-well plates. Subsequently, each group was incubated in a dark room at 25°C for 30 minutes. Dopachrome levels were assessed by measuring absorbance at 475 nm using a microplate reader. The percentage inhibition of tyrosinase activity was calculated using the following equation.

$$\% \text{ Tyrosinase inhibition} = [(A\text{-}B)\text{-}(C\text{-}D)/ (A\text{-}B)] \times 100$$

Test for cytotoxic activity

Cell cultures

Human colon adenocarcinoma (HT29) cells were utilized for cancer cell experiments, while African green monkey kidney (Vero) cells served as normal cell lines for cytotoxicity assays. HT29 and Vero cell lines were obtained from Dr. Porntipa Picha, Research Division, National Cancer Institute, Bangkok. The cells were cultured in Roswell Park Memorial Institute 1640 (RPMI 1640) medium supplemented with 8% (v/v) fetal bovine serum (FBS) and gentamicin in a 5% CO_2 incubator at 37°C.

MTT colorimetric assay

In vitro, cytotoxic activity was assessed using Mosmann's MTT colorimetric assay (1983) with minor adjustments and Poeaim *et al*. (2016). Briefly, Cells were trypsinized from the early exponential phase of the cell culture flask and then diluted with RPMI 1640 medium containing 5% (v/v) fetal bovine serum (FBS). The cells were seeded at a density of 1.5×10^5 cells in 100 µL per well in 96-well plates and then incubated in the CO_2 incubator with 5% CO_2 at 37°C for 24 hours. Following overnight incubation, cells were exposed to 100 µL of methanolic extract at concentrations ranging from 62.5 to 1000 µg/mL (final concentration in each well) and were further incubated for 20 hours. Dimethyl sulfoxide (DMSO) was the negative control, while the anticancer drug mitomycin C (MMC) was employed as the

positive control. Subsequently, 50 µL of MTT solution (2 mg/mL in phosphate buffer saline) was added to each well and incubated continuously for 4 hours. The supernatant was then aspirated from each well, and 100 µL of dimethyl sulfoxide (DMSO) was added to dissolve the formazan crystals. The absorbance was measured at 570 nm using a microplate reader (Anthos MultiRead 400, Biochrom, UK). The percentage of cell growth inhibition was calculated as follows: Inhibition of cell growth (%) = [($Abs_{Control}$-Abs_{Sample}) / $Abs_{Control}$] × 100. $Abs_{Control}$ is the absorbance value of cells without extracts, and Abs_{Sample} is the absorbance value of cells with extracts. The 50% inhibitory concentration (IC_{50}) of extracts against various cell lines was determined using GraphPad Prism 6.0 software.

Statistical analysis

All experimental measurements were conducted in triplicate and presented as the mean ± standard deviation (SD). The data were analyzed using Statistical Package for the Social Sciences (SPSS) version 17.0.

Results

Extraction yield

The methanolic extract yield of flesh and peel of santol fruits was 25.24% and 7.93%, respectively. Furthermore, the methanolic extracts of each part from santol fruits by maceration method showed different appearances. The methanolic extract from the flesh are shown to be an orange-brown color and viscous, the methanolic extract from the peel is dark orange-brown and is a powdered solid.

Phytochemical screening

The phytochemical screening results revealed the presence of tannin, alkaloid, saponin, betacyanin, and coumarin, as shown in Table 1.

Antibacterial activity

The methanolic extracts from the santol fruit's flesh and peel were evaluated for antibacterial activity against *B. cereus* and *S. aureus* (gram-positive bacteria), and *E. coli* (gram-negative bacteria). The results indicated that extracts from both the flesh and peel, at a concentration of 2000 µg/disc, exhibited antibacterial activity against *B. cereus* and *S. aureus*, as detailed in Table 2. Nonetheless, there was no observed inhibitory effect against *E. coli*. Notably, the peel extracts demonstrated the highest activity at 3000 µg/disc,

yielding inhibition zones of 13.20±0.50 mm and 10.71±0.70 mm for *B. cereus* and *S. aureus*, respectively.

Table 1. Phytochemicals found from methanolic extract of flesh and peel of santol fruits

Group of compounds	Method/ test reagents	Test results	
		Flesh	Peel
Tannin	Gelatin solution	+	+
	Gelatin salt solution	+	+
	$FeCl_3$	+	+
Alkaloid	Dragendroff's	-	+
	Mayer's	-	+
	Wagner's	-	+
Saponin	Froth test	+	+
	Hemolysis test	+	-
Anthocyanin	Anthocyanin	-	-
	Betacyanin	+	+
Coumarin	Coumarin test	+	+

Note + change ; -no change

Table 2. The inhibition zone of the methanolic extracts from the flesh and peel of santol fruit at different concentrations, along with data for gentamicin

The methanolic extracts from Santol fruits	The concentration (µg/disc)	Inhibition zone (mm)		
		Gram-positive		Gram-negative
		B. cereus	*S. aureus*	*E. coli*
Flesh	1000	-	-	-
	2000	6.42±0.40	6.80±0.20	-
	3000	8.20±0.30	8.20±0.40	-
Peel	1000	7.00±0.30	7.15±1.15	-
	2000	10.90±0.23	10.60±0.57	-
	3000	13.20±0.50	10.71±0.70	-
Gentamicin	10 µg/disc	31.45±0.32	23.95±0.11	24.25±0.35

The data are expressed as mean±SD

Antioxidant activity

The relationship between the concentrations of methanolic extracts from the flesh and peel of santol fruit and the corresponding percentage of antioxidant activity as measured by DPPH and ABTS methods is shown in Figures 2 A and 2 B, respectively. The IC_{50} values for the free radical scavenging activity of the methanolic extract from santol fruit peel were 30.00 µg/mL and 48.00 µg/mL using the DPPH and ABTS methods, respectively. In contrast, the IC_{50} values for the extract from the flesh were 124.00 µg/mL and 217.00 µg/mL for the DPPH and ABTS methods, respectively. The IC_{50} values for the Trolox standard reagent were 43.61 µg/mL and 80.12 µg/mL, as detailed in Table 3.

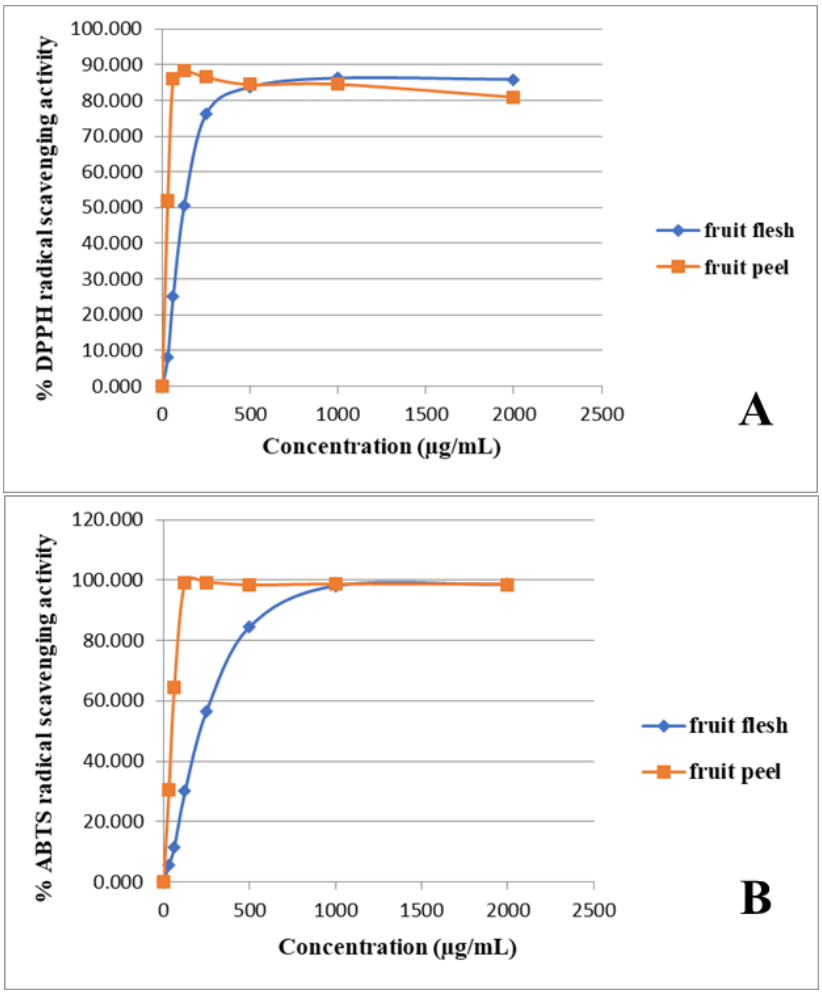

Figure 2. The relationship between the concentrations of methanolic extracts from the flesh and peel of santol fruit and the corresponding percentage of antioxidant activity as measured by DPPH (A) and ABTS (B) methods.

Table 3. Antioxidant capacity and 50% inhibitory concentration (IC_{50}) of the methanolic extracts from the flesh and peel of santol fruit

Methanolic extracts from santol fruit	Antioxidant capacity		IC_{50} values (µg/mL)	
	DPPH (mgTE/g extract)	ABTS (mgTE/g extract)	DPPH	ABTS
Santol flesh	207.42	261.99	124.00	217.50
Santol peel	546.75	810.99	30.00	48.00
Trolox	-	-	43.61	80.12

Anti-tyrosinase activity

According to the dopachrome method, the extracts from the flesh and peel of santol fruit demonstrated concentration-dependent anti-tyrosinase activity. In addition, The peel extract showed higher tyrosinase inhibitory activity than the flesh extract, with 76.37% at 1000 µg/mL (Table 4).

Table 4. The percentage of tyrosinase inhibition of the methanolic extracts from santol fruits

The methanolic extracts from santol fruits	Tyrosinase inhibition (%)
Flesh 500 µg/mL	24.65±1.47
Flesh 1000 µg/mL	51.16±1.92
Peel 500 µg/mL	62.08±2.15
Peel 1000 µg/mL	76.37±2.69

The data are expressed as mean±SD

Cytotoxicity activity

It showed that the methanolic extract of the santol fruit peel was more cytotoxic than the fruit flesh at the same concentrations (Table 5).

Table 5. The average percentage of cytotoxicity to Vero and HT-29 cell lines tested with methanolic extract of santol fruit flesh and peel at different concentrations

Test	Concentration (µg/mL)	Average percentage of cytotoxicity on cell lines	
		Vero	HT-29
Santol fruit flesh	125	4.43±0.06	-12.93±0.09
	250	3.51±0.05	7.22±0.18
	500	9.37±0.01	5.17±0.18
	1000	20.91±0.06	4.88±0.14
	2000	17.98±0.09	2.67±0.18
Santol fruit peel	125	12.67±0.11	-16.56±0.05
	250	30.20±0.03	12.10±0.17
	500	26.77±0.05	13.14±0.06
	1000	26.39±0.06	34.29±0.01
	2000	37.18±0.07	47.39±0.03

Discussion

Five phytochemicals, namely tannin, alkaloid, saponin, anthocyanin, and coumarin, were subjected to testing. Tannin, alkaloid, betacyanin, and coumarin were identified in the methanolic extract of santol fruit peel. Indeed, the absence of saponin in the santol fruit peel extract is indicated by the positive froth test and negative hemolysis test results. On the contrary, the methanolic extract of santol fruit flesh contained tannin, saponin, betacyanin, and coumarin. Saponin was exclusively detected in the flesh extracts, while alkaloid was specifically found in the peel extracts. The phytochemicals, including saponin, flavonoids, alkaloids, tannin, steroids, phenol, and cardiac glycoside, were discovered in more significant quantities in the seeds compared to the leaves, as reported by Ekeleme *et al*. (2016). Interestingly, these phytochemicals were found in higher concentrations in cold and warm water extracts than in the ethanolic extract. While a quantification study was not conducted in this study, it was observed that various parts of the fruit contained distinct quantities and phytochemical constituents within the methanolic extract.

For antibacterial activity, it was observed that the extract concentration at 2000 µg/disc exhibited inhibitory effects on the growth of *B. cereus* and *S. aureus*, while no inhibitory effect was noted on the growth of *E. coli*. The peel extracts exhibited a slightly broader inhibition zone on both bacteria than the flesh extracts. However, neither the flesh nor the peel extracts demonstrated antibacterial activity against *E. coli* at any tested concentrations. The antibacterial activity of the methanolic extract from both the flesh and peel of santol fruit in this study was observed to be less potent when compared to the methanolic extract of santol leaf extract, which has shown antibacterial activity against *Staphylococcus mutans* (Pambudi *et al*., 2021) and mahogany seed (*Swietenia macrophylla*), a plant from the same family. Maiti *et al*. (2007) reported significant antibacterial effects against *B. cereus*, *K. pneumoniae*, *E. coli*, and *S. aureus.*

Methanolic extract of santol fruit peel was found to be 4.15 and 4.53 times higher potency than santol fruit flesh and 1.45 and 1.67 times higher potency than Trolox reagent by DPPH and ABTS methods. Free radical scavenging property on DPPH of the flesh and peel methanolic extract was found at 207.42 and 546.75 mgTE/g extract and on ABTS at 261.99 and 810.99 mgTE/g extract. The peel extract was more potent on the free radical scavenging property than the flesh extract in both methods. The methanolic extract of santol fruit peel in our study, which had IC_{50} at 30.00 µg/mL was the most potent in free radical scavenging properties when compared to the extract of the *Opuntia stricta* fruit peels (Koubaa *et al*., 2015), extract of flesh and peel of *Actinidia chinensis* (kiwi) fruit (Alim *et al*., 2019).

Typically, the healthy cells exhibited normal morphologies and adhered well to the substrate. After 20 hours of incubation with the methanolic extract

of santol fruit, cells shrank in a round shape but still adhered to the substrate. After adding MTT for four hours, Formazan crystals were found in control cells, which reflected alive cells, while in cells tested with the methanolic extract of santol fruit peel at 2000 µg/mL, the Formazan crystals were found only partly, which reflected partly alive cells. Aisha *et al*. (2009) reported cytotoxicity of the extract of santol bark on human colorectal cancer cells (HT-29) for IC_{50} at 51.18 µg/mL, including the report from Wijaya (2022) that showed cytotoxic activity in a human myeloid leukemia cell line (HL-60), human breast cancer cell line (MCF-7), and human colon carcinoma cell line (HCT-116). Compared to our study, the methanol extract of santol fruit peel at 2000 µg/mL has only 47.39% cytotoxicity. The IC_{50} of the methanolic extract of santol fruit flesh and peel will be higher than 2000 µg/mL. Nevertheless, in a study by Li *et al*. (2013), extracts from the peels, pulps, and seeds of 61 fruits were investigated for their *in vitro* anti-proliferative activities on human lung cancer cells (A549), human breast cancer cells (MCF-7), human hepatoma cells (HepG2), and human colon cancer cells (HT-29). The findings indicated varying anti-proliferative capacities among fruits and parts of the same fruit.

It is concluded that phytochemical, antibacterial, antioxidant, and cytotoxicity of the methanolic extracts of santol fruit flesh and peel showed that the methanolic extract of santol fruit contains tannin, alkaloid, saponin, betacyanin, and coumarin. However, saponin was exclusively detected in the flesh extracts, while alkaloid was specifically found in the peel extracts. For antibacterial activity, it was observed that the extract concentration at 2000 µg/disc exhibited inhibitory effects on the growth of *B. cereus* and *S. aureus*, while no inhibitory effect was noted on the growth of *E. coli.* For antioxidant activity, the methanolic extract of santol fruit peel had higher free radical scavenging properties than the flesh extract for which the IC_{50} from DPPH and ABTS methods were 30.00 and 48.00 µg/mL. The cytotoxicity activity using MTT assay on normal monkey kidney cells (Vero) and human colorectal cancer cells (HT-29) found that the methanolic extract of santol fruit peel was cytotoxic at 125-2000 µg/mL. At a 2000 µg/mL concentration, the cytotoxicity towards Vero and HT-29 cells was 37.08% and 47.39%, respectively. Given the observed high antioxidant activity, exploring additional potential benefits, such as anti-inflammatory properties, becomes intriguing. These findings could contribute to the development of cosmo-pharmaceutical and medicinal products and serve as fundamental knowledge for selecting fruits for optimal daily consumption. Additional investigations of this plant should focus on isolating pure chemical constituents and evaluating *in vivo* biological activities. These efforts aim to pave the way for developing high-value natural pharmaceutical products.

Acknowledgements

The authors would like to thank Miss Chanisara Thiankanthet, Miss Arrirat Bututham, and Mr. Pollawat Luengsawat for encouraging my research.

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(Received: 5 November 2023, Revised: 22 January 2024, Accepted: 28 February 2024)