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Antioxidant and Cytotoxic Activities of Ethanolic Extracts of Mammea siamensis Flower

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Abstract: *In this work, the phytochemical content, antioxidant and cytotoxic activities of flower-derived ethanolic extracts of Mammea siamensis were examined. The yield crude of the semi-solid yellowish-brown extract was 11.13±0.11% w/w with a characteristic odor. Total phenolic content was determined as 115.27±0.003 μg GAE/mg dry weight and indicated that the extract was very rich in bioactive phenolics. However, moderate antioxidant activity was observed on DPPH radical scavenging (IC_{50}=35.92±1.127 μg/ml) being seven times weaker than that of ascorbic acid and also weak nitric oxide scavenging (IC_{50}=493±1.033 μg/ml). The cytotoxicity tests showed a dose-dependent toxicity in lesion fibroblasts, HaCaT and B16F1 melanoma cells, with fibroblasts being the less sensitive. Cytotoxicity was dramatic at concentrations ≥ 50 μg/ml for all cell lines and quasi-extinction was observed for concentrations included between 500 to 1000μg/ml. These results suggest that the flowers of Mammea siamensis can be a source of phenolic antioxidants with selective cytotoxicity and could be employed in pharmaceutical or cosmeceutical formulations.*

Keywords: *Mammea siamensis, Antioxidant activity, Cytotoxicity*

INTRODUCTION

Mammea siamensis, known as "Saraphi" in Thai, is a member of the Calophyllaceae family whose origins can be traced to Thailand, Laos, Vietnam and Cambodia. This is an evergreen tree that generally grows to a height of 10–15 meters, with dense foliage and simple opposite leaves that are fragrant when crushed and yellowish white in color with each flower having 4-5 petals and growing in clusters between January to March. The fruit is spindle-shaped, edible and yellow when ripe. Mammea siamensis flowers have long been used in the form of herbal teas and Thai traditional medicine. Nutritionally, the plant is rich in bioactive compounds such as coumarins, xanthones and flavonoids that were demonstrated for antioxidant capacity and anticancer activity [1]. Phenolic and flavonoid content of flower extracts, which have been reported to exhibit antioxidant activity [2-3], are recently under investigation. The extracts have shown strong free radical scavenging activity in DPPH assays (EC_{50} = 10.17 μg/mL) and a significant inhibition of lipid peroxidation (IC_{50} = 0.43 μg/mL). In addition, methanolic flower extracts have shown remarkable NO production suppression activity in activated macrophage, because of certain coumarins that inhibited the expression of iNOS [4]. Cytotoxic test in vitro cell assay has shown that some isolated compounds of Mammea siamensis exert antiproliferative activity against a variety of cancer cells, implying their potentiality towards anticancer nature [1,5]. The interest of our research group in Mammea siamensis flower and other Thai medicinal plants is based on their traditional use and bioactive potential. The objective of the present study was to study in vitro antioxidant activity and cytotoxicity of Mammea siamensis extracts for screening active principles that can be used as major components in cosmetics. Because of the antioxidant and anti-aging effects of phenolic and flavonoid compounds which were found in Mammea siamensis, it is very interesting for the future use as a natural, effective, and safe product for skincare and cosmetic industry [1,6].

MATERIALS AND METHODS

Extraction of plant material

The flowers of Mammea siamensis were purchased from the Chaokrompoe herbal store, Thailand. The flowers were grounded into fine powder after air drying. The powder obtained was rinsed three times with 95% (v/v) ethanol at room temperature for 72 hours. This extraction was repeated on 2 more occasions and the pooled extracts filtered. The solvent was subsequently evaporated under reduced pressure (40–45°C), and the extract was finally freeze-dried to remove residual solvents, thus obtaining a crude extract that was frozen at −20°C until analysis.

Total phenolic content

Total Phenolic Content (TPC) in the extract of the Mammea siamensis was determined with the Folin–Ciocalteu method, a recognized colorimetric assay for evaluating phenolic compounds in plant extracts. In the present study, a calibration curve was run using gallic acid as the reference standard in the concentration range of 12.50 – 800.00µg/mL according to Nakyai et al., (2021) [7]. This procedure is based on the electron-transfer of phenolic compounds contained in the sample that reduce the Folin-Ciocalteu reagent under alkaline medium to develop a blue complex. This complex form has an intensity measured spectrophotometrically at about 765 nm that varies linearly as a function of the phenolic content. These results are presented as mg GAE/g of extract, which allows for average comparison among the samples. This method provides accurate determination of total phenolics, which are important to the antioxidant activity of plant samples.

Antioxidant activity

The antioxidant effect of the Mammea siamensis extract was comprehensively assessed by means of three well-known in vitro methods which detect different mechanisms of action related to antioxidation. The hydrogen atom and electron donating ability were analyzed by 2,2-diphenyl-1-picrylhydrazylfree radical (DPPH) scavenging assay. On the other hand, ABTS (2,2′-azinobis (3-ethylbenzothiazoline-6-sulfonic acid)) assay revealed information on extract scavenging capacity for hydrophilic and lipophilic radicals via an electron transfer. The extract's reducing potential (ability to reduce ferric ions to ferrous ion which is indicative of the antioxidant activity) was also determined by FRAP assay. The performed methods were reproducible and used identically, as all three assays applied similar protocols as those described in Nakyai et al. (2021) [7]. Ascorbic acid was used as a classic antioxidant compound of natural origin and as positive control to show the sensitivity levels of the assays and set up reference to compare with. Percentage inhibition of radicals was read and IC_{50} (concentration yielding 50% radical scavenging) values were determined by GraphPad Prism version 10.0 for accurate dose-response relationship analysis and statistical comparison.

Cytotoxic activity

Cell culture condition

The methodology employed three different cell types, representative elements of skin structure. Normal human primary fibroblasts were grown in low-glucose Dulbecco's Modified Eagle Medium (DMEM), while both keratinocytes (HaCaT cell line) and melanocytes (B16F1 cell line) were cultured in high-glucose DMEM. All culture media were supplemented with 10% fetal bovine serum for cell nutrition, 1% penicillin-streptomycin to avoid bacterial contamination and 0.4% fungizone for antifungal protection. The cells were maintained in a humidified incubator with 5% CO_2 at 37°C. When the dishes were nearly 80% confluent, cells were passaged using standard methods, performed by washing in PBS followed by trypsin-EDTA treatment (0.25%) for detachment and resuspension into fresh medium to be seeded onto 96-well plates in which the experimental protocols were applied [7].

MTS assay

Cytotoxicity was assessed using MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxy methoxy phenyl)-2-(4-sulfophenyl) 2H-tetrazolium) colorimetric assay that determines the water-soluble formazan dye whose formation is directly proportional to the metabolic activity of cells. It followed the adopted procedures referred to by Nakyai et al. (2021) [7]. The cytotoxic (50% inhibitory concentration; IC_{50}) potencies across all skin cell lines were used to quantify the activity. These calculations were performed using the GraphPad Prism 10.0 and used for the systematic validation with statistical robustness in description of dose-response relationships.

Statistical analysis

All results are presented as mean±standard deviation (SD). Differences among groups were analyzed by one-way analysis of variance (ANOVA) with Tukey's post hoc test for multiple comparisons. $p< 0.05$ was

considered statistically significant. All statistical analyses were carried out with GraphPad Prism (version 10).

RESULTS

Extraction yield

Extraction of the Mammea siamensis flower, as shown in Figure 1, was performed by ethanolic maceration with crude extract exhibiting a semi-solid deep yellowish brown appearance with the scent peculiar to that of floral mixture. The extraction efficiency achieved was 11.13 ± 0.11% w/w.

Figure 1: shows dried flowers of Mammea siamensis

Total phenolic content

The amount of total phenolic content in Mammea siamensis flower calculated is 115.27±0.003 µg GAE/mg dry weight as shown in Table 1. This value shows a high concentration of bioactive phenolics. Quantification was based on the Folin-Ciocalteu assay with calibration equation y = 0.0014x + 0.0026 (R^2 = 0.9999). In addition, high correlation coefficient indicates that the method is linear and accurate. It shows a good linear correlation between the absorbance and concentration of gallic acid equivalent for determination of total polyphenol content. Phenolic content reported in the current study is in agreement with previous investigations conducted on Mammea siamensis. A comparison conducted by Srisuwan et al. (2018) [8] found 43.34 ± 0.51 mg GAE/g dry weight in Mammea siamensis flowers, and Panchakul (2020) [9] reported the value of 144.28±4.07 mg GAE/g; it appears that particle conversion from g to g measured are appropriate for comparability with similar existing study ranges at lower and higher end which validates reproducibility and accuracy of analytical method applied here.

Antioxidant activity

DPPH radical scavenging

The DPPH radical scavenging activity of Mammea siamensis flower extract had an IC_{50} value of 35.92 ± 1.127 µg/ml, indicating a moderate antioxidant ability compared with the positive control, ascorbic acid (IC_{50} = 5.15 ± 1.039 µg/ml), shown in Table 1. It implies that Mammea siamensis flower possesses about 7 times lower scavenging capacity than ascorbic acid. However, this kind of activity can be impressive for a plant extract since generally natural products have higher IC_{50} values as compared to synthetic antioxidants. DPPH method measures the potential of compounds to donate hydrogen or electron to quench the stable colorless DPPH radical, whose reduction causes change in color from purple to yellow [10]. The discrepancy may result from the differences in polarity of extracts because DPPH scavenging activity was found to vary among different parts of Mammea siamensis; for example, flowers show a DPPH scavenging activity amounting to 21.77 ± 0.21 mg ascorbic acid equivalents/g extract [3]. Moreover, ethanolic extract from Mammea siamensis shows high efficacy in radical scavenging activities with very low EC_{50} values (8.54 µg/ml) as compared to butylated hydroxyl toluene (BHT; EC_{50} = 11.66 µg/ml) [11]. Mammea siamensis shows a marked antioxidant activity due to its high content in phenolic compounds, specially coumarins and xanthones that contribute for free radical scavenging [3,12]. These results indicate that Mammea siamensis flowers contain potent antioxidants with DPPH radical scavenging activity.

Nitric oxide scavenging

The nitric oxide scavenging assay of Mammea siamensis flowers demonstrated an IC_{50} value of 493±1.033 µg/ml, which was relatively lower neutralizing potential to that of ascorbic acid (IC_{50}=0.35±1.247 µg/ml) (Table 1). This IC_{50} value represents a 1400-fold less potent activity compared to the positive control, demonstrating that direct NO scavenging is not the major antioxidant mechanism of Mammea siamensis flowers. Nitric oxide scavenging assay, the nitric oxide scavenging potential was determined by measuring the inhibition of accumulation of nitrite ions produced from sodium nitroprusside in competition with the atmospheric oxygen, that is mediated through generation of NO radical [13]. But available information shows that Mammea siamensis possesses an inhibitory effect on NO production in various ways. It has been reported that the methanolic extracts of Mammea siamensis flower significantly

suppressed nitric oxide production in LPS-stimulated RAW 264.7 cells, wherein some-what-pure coumarins showed IC_{50} values between 0.8 and 7.9 μM toward lipopolysaccharide-induced nitric oxide production inhibition (Morikawa et al., 2012). Some compounds, such as mammeasins and other coumarins inhibited activation leading to inhibition of iNOS expression [4]. On the other hand, ethanolic extracts of Mammea siamensis gave nitric oxide inhibitory activity in cellular models when those of water did not [11]. These results, together, indicate that although the Mammea siamensis flower extract may possess limited direct action in scavenging NO radical, it exhibits strong anti-inflammatory activity as an inhibitor of NO production pathway rather than a free-radical scavenger.

Table 1: Shows the result of total phenolic content and antioxidant activity of Mammea siamensis extract

Sample	Total phenolic content (ug GAE/mg of DW plant)	IC_{50} (ug/ml)	
		DPPH radical scavenging	Nitric oxide scavenging
Mammea siamensis	115.27 ± 0.003	35.92 ± 1.127	493 ± 1.033
Ascorbic acid	-	5.15 ± 1.039	0.35 ± 1.247

*Ascobic acid was used as positive control

Cytotoxicity

fibroblast cell

The cytotoxicity of Mammea siamensis flower extract on the fibroblast cell line showed a clear dose-dependent cytotoxic response and threshold. At lower concentrations of 5–25 μg/ml, the cell viability was higher than that of control group (>100%), suggesting good biocompatibility. At relatively high concentrations (50 μg/ml) the viability fell down to ≈85%, while nearly complete cell death was achieved at the concentrations of 500-1000 μg/ml (<5% viability), as demonstrated in Figure 1(a). These findings are in line with previous research concerning Mammea (americana), where the seed extract exhibited cytotoxicity against MRC-5 human fibroblasts with an IC_{50}= 48.98 μg/ml [16]. Furthermore, coumarins derived from Mammea siamensis flowers have been shown to possess anti-proliferative effects via an apoptotic pathway [1,14,15].

HaCaT

Results of the toxic effect on HaCaT cells in vitro was very obvious, and the decrease of HaCaT cell viability with the increase of the dos age of the tested compound showed a good dose-dependence relationship. At concentrations of 1–25 μg/ml (Figure 1(b)), cell viability was consistent with control and no significant cytotoxicity was observed. In contrast, at 50 μg/ml and higher concentrations there was a concentration-dependent reduction in viability with survival rates below the otherwise quantitatively determined 50% control value 100 μg/ml and almost complete inhibition at 250 μg/ml. These results agree with whoever pointed out that higher concentration of cytotoxic agents strongly inhibits HaCaT cell proliferation as they emphasize the importance of their prevailing concentrations when testing a compound for safety in dermatology [17].

B16F1

The investigation discloses a dose dependent cytotoxic activity against B16F1 melanoma cells, i.e., the cell viability reduced from around 120% (control) to nearly death at 1000 ug/ml (Figure 1(c). Together, these results fit with known cytotoxicity profiles on B16F1 cells and demonstrate that they are an appropriate preclinical model for melanoma [18-19]. The statistically significant differences between treatments (as denoted by letter characters) indicate that concentration-dependent effects are evident, much like previous studies described in 1,4-naphthoquinone and lidamycin [18-19]. The possible underlying mechanisms may be associated with oxidative stress, and apoptosis or cell cycle arrest as B16F1 studies have shown [18-19]. IC_{50} at the mid-range (50–100 μg/ml) implies that this compound is moderately active. This discovery should lead to further evaluation of the novel molecular targets and therapeutic opportunities against melanoma. The concentration of the tested compound percentage of cell viability curve with respect to three different cell types such as HaCaT, B16F1 and fibroblast are shown in Figure 1(d). % cell viability decreases for all the cell types in a dose dependent cytotoxicity manner with increased concentration of the compound. Of these three cell types, fibroblasts (blue triangles) proved to be the most resistant to the compound, as they were more viable at higher concentrations compared with HaCaT (black circles) and B16F1 cells (red squares). On the other hand, cytotoxicity of HaCaT cells and B16F1 cells is more significant, indicating the higher susceptibility of these two cell lines to it. These results

indicate that the compound has different levels of cytotoxicity according to cell type, and fibroblast is less sensitive compared with HaCaT and B16F1 cells.

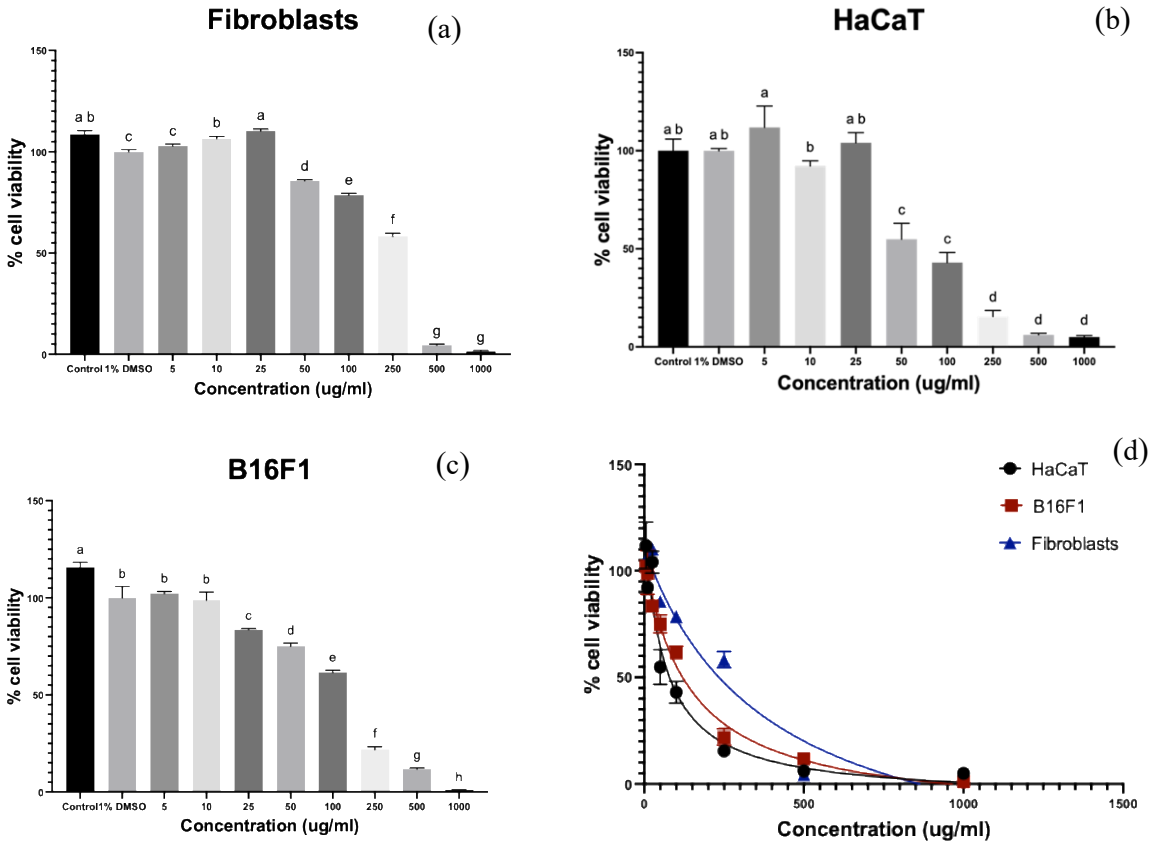

Figure 2: Shows the effects of various concentrations of the tested compound on cell viability in three different cell lines: (a) Fibroblasts, (b) HaCaT keratinocytes, and (c) B16F1 melanoma cells and (d) Dose-response curves summarizing the cytotoxic effects across all three cell lines. Data are presented as mean ± S.D. (n = 3). Different letters above the bars indicate statistically significant differences between groups ($p < 0.05$).

DISCUSSION

The overall screening of Mammea siamensis flower extracts generates a hopeful bioactive activity for future research with mild therapeutic applications. The ethanolic extract extracted 11.13% w/w of crude extracts containing high phenolic contents (115.27 µg GAE/mg) due to the significant antioxidant activities of this plant material. The DPPH radical scavenging activity (IC_{50} = 35.92 µg/ml), on the other hand, indicates moderate free radical neutralizing potential which was lesser by about seven times than that of ascorbic acid. However, when it comes to direct either through Fenton reaction or other possible chemical neutralization of NO produced only very low IC_{50} value = 493 µg/ml was observed that means partial involvement in the composition used via iNOS inhibition pathways for anti-inflammatory activities. Cytotoxicity evaluation in three different cell lines showed different sensitivity of fibroblasts, HaCaT and B16F1. Overall, these results reveal concentration-dependent effects that may be exploited for selective therapeutics with acceptable safety profiles at lower concentrations. Taken together, our results suggest that the Mammea siamensis flowers extract has mild and controllable bioactivity which could be suitable in development for therapeutic and cosmetic uses. According to cytotoxicity profiles of the extract, an appropriate concentration range for cosmetic preparations should not be higher than 25 µg/ml in order to be safe on all tested cell types. Between 5 and 25 µg/ml, all of the cell lines preserved viability over 100% in nontoxicity without significant cytotoxic influence for excellent topical biocompatibility. The cytotoxic concentration of 50 µg/ml, where pronounced cytotoxicity occurs in various cell lines, provides a wide safety range for use in cosmetic formulations. This study would respect the antioxidant positive effect of the phenolic compounds and avoid possible negatives effects on skin cells, in particular keratinocytes (HaCaT), that are considered as one target cell when applied topically for

a cosmetic purpose. Thus cosmetics containing Mammea siamensis flower extract below 25 μg/ml in the form of formulations would have excellent safety, efficacy properties.

CONCLUSION

This study elucidates the interesting bioactivity of Mammea siamensis flower extract, which gave a fair yield (11.13±0.11% w/w), significant total phenolic content (115.27±0.003 μg GAE/mg) and moderate antioxidant activity as depicted from DPPH (IC_{50}=35.92±1.13μg/ml) and nitric oxide scavenging assay (IC_{50}=493±1.03μg/ml). Results of cytotoxicity evaluation in fibroblast, HaCaT and B16F1 cells showed that concentrations 100%), evidencing excellent biocompatibility and nontoxic characteristics. Noticeable cytotoxic effects were seen at 50 μg/ml and higher concentrations. These concentration ranges would be both safe and effective, which suggest that Mammea siamensis flower extract could potentially be used as cosmetics or therapeutic ingredient, protecting skin from oxidative stress and showing mild cytotoxic effects.

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Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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