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Original article

Study on preliminary screening of the triterpenoid constituents and *in vitro* tyrosinase inhibitory activity of dragon fruit flowers (*Hylocereus undatus* (Haw.) Britton & Rose)

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Abstract: The flowers of *Hylocereus undatus* (Haw.) Britton & Rose have been reported *in vitro* antioxidant and tyrosinase inhibitory activities. This study screened preliminarily the triterpenoid constituents and evaluated *in vitro* tyrosinase inhibitory activity of *H. undatus* flowers. *H. undatus* flowers were harvested from Binh Thuan Province, Vietnam at four different flowering stages, and their five separated parts (stamen, pistil, petals, ovary, and sepals) were extracted with ethanol. Triterpenoids were identified in the extracts by thin-layer chromatography and Liebermann - Burchard reaction. Tyrosinase inhibitory activity was evaluated using the dopachrome method with L-tyrosine substrate and kojic acid as the positive control. Results showed that at the different flowering periods, there was the formation of different parts of the flowers. The triterpenoid compounds are the main constituents in the *H. undatus* flower extracts. The 70% ethanol extract from *H. undatus* flower at the stage of 2 - 3 days before blooming exhibited the strongest tyrosinase inhibitory activity with IC_{50} value of 266.4 µg/mL compared to that of 7.60 µg/mL of kojic acid. In the case of separation of flower parts, 70% ethanol extracts of each part inhibited weakly the tyrosinase enzyme. In conclusion, the present study provided information about the morphological characteristics of *H. undatus* flower collected from Binh Thuan Province, Vietnam. Triterpenoid was found as the main constituents of the ethanolic extracts of *H. undatus* flower. The 70% ethanol extract from whole *H. undatus* flower at the stage of 2 - 3 days before blooming exhibited strong tyrosinase inhibitory activity.

Keywords: *Hylocereus undatus* (Haw.) Britton & Rose; dragon fruit flower; triterpenoid; tyrosinase inhibitory activity.

1. INTRODUCTION

Melanin is responsible for the pigmentation of human eyes and skin, secreted by melanocytes in the dermis basal layer. In response to ultraviolet B-irradiation, melanocyte synthesizes melanin. Under normal physiological conditions, melanin pigmentation can shield from UV radiation, inhibit photocarcinogenesis and affect vitamin D3 synthesis. In contrast,

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melanin hyperpigmentation causes dermatological problems. As a key enzyme for melanin biosynthesis via oxidative reactions of tyrosine, tyrosinase has been considered an important target for developing therapeutic agents of pigmentation disorders. Therefore, natural and synthetic tyrosinase inhibitors as whitening and anti-hyperpigmentation agents have been used as depigmentation ingredients of cosmetic and medicinal products [1].

Recently, dragon fruit with whitish pulp [*Hylocereus undatus* (Haw.) Britton & Rose] has been popularly grown more and more in Vietnam. At the onset of flowering, groups of three to five buds are formed from the stem margins; two and three of these may develop into flower buds. The green cylindrical flower buds reach about 25 - 30 cm after 17 days when anthesis occurs. The flower opens rapidly, closes after pollination and thereafter flower begins to wilt. One of the techniques to help *H. undatus* produce good quality fruit and increase their resistance to adverse external conditions is flower thinning by the removal of floral buds or by not pollination the flowers.

The *H. undatus* fruit rich in antioxidants, vitamin C, phosphorus, calcium considered as a healthy fruit due to medicinal properties has been reported to prevent cancer, diabetes, and bleeding, reduce cholesterol and high blood pressure, develop strong bones, teeth, and skin [2]. According to Li et al. (2019), trypsin treatment in *H. undatus* fruit storage could increase superoxide scavenging activity of its antioxidant enzymes; leading to improving cell membrane integrity and reducing cell damage [3]. The dragon fruit peel powder rich in dietary fiber, phenolics improved the nutritional quality of chicken nuggets by decreasing lipid oxidation [4]. Moreover, dietary tannins and saponins from dragon fruit peel powder have been shown to reduce greenhouse gas production measured as decreases in methane production in the ruminal fermentation [5]. *H. undatus* foliage and peels contain phenolic compounds and have antioxidant activity; hence these raw materials could be a potential natural antioxidant in pharmaceutical and food applications [6]. Compared to Hylocereus polyrhizus, *H. undatus* peel showed similar bioactive compounds of tannins, flavonoids, phenolic acids, organic acids, nucleotides, lignans, and relatively low accumulation of alkaloids, amino acids, lipids [7]. Besides fruit, the *H. undatus* flower buds have been used as a vegetable to make soups or mixed in salads or tea. In traditional medicine, *H. undatus* flowers have been used to treat bronchitis, tuberculosis and drunkenness [2]. Some studies evaluated the in vitro antioxidant and tyrosinase inhibitory activities of the extracts from *H. undatus* flowers [8, 9]. For these reasons, the *H. undatus* flowers could be an abundant source of raw material possibly used in cosmetic and pharmaceutical industries. Moreover, according to Ly Kieu Huong and Tran Thi Van Anh (2020), the triterpenoids could be the main chemical constituents of *H. undatus* flowers collected from Binh Thuan Province, Vietnam [10]. However, there has been not a scientific report about the tyrosinase inhibitory activity of this Vietnamese plant material. Therefore, this study aimed to screen preliminarily triterpenoid constituents and evaluate in vitro tyrosinase inhibitory activity of ethanolic extracts of *H. undatus* flowers harvested from Binh Thuan Province, Vietnam.

2. MATERIALS AND METHOD

2.1. Plant materials

The fresh flowers of *H. undatus* were collected from Phan Thiet Town, Binh Thuan Province, Vietnam in December 2017. The sample was authenticated by Assoc. Prof. Tran Thi Van Anh by comparing the botanical characteristics with the data in the botanical taxonomy documents. The voucher specimens were kept at the Department of Pharmacognosy, Faculty of Pharmacy, University of Medicine and Pharmacy at Ho Chi Minh City, Ho Chi Minh City, Viet Nam.

H. undatus flowers (HUF) at 4 different periods of flowering including 5 - 6 days bud, 8 - 15 days bud, 2 - 3 days before or after blooming and pollination (noticed as 1, 2, 3, 4, respectively) were collected in December 2017 and HUF3 collected in June 2020 from Phan Thiet Town, Binh Thuan Province, Vietnam (supplied by Lavite company, Binh Thuan Province, Vietnam).

2.2. Description of H. undatus flower characteristics

The macroscopic features of fresh *H. undatus* flowers were examined. The photographs were taken using Canon digital camera.

2.3. Preparation of ethanolic extract from H. undatus flowers

Figure 1. *Hylocereus undatus* flowers at different 4 flowering periods: 5-6 days old (HUF1), 8-15 days old (HUF2), 2-3 days before and after blooming (HUF3 and HUF4)

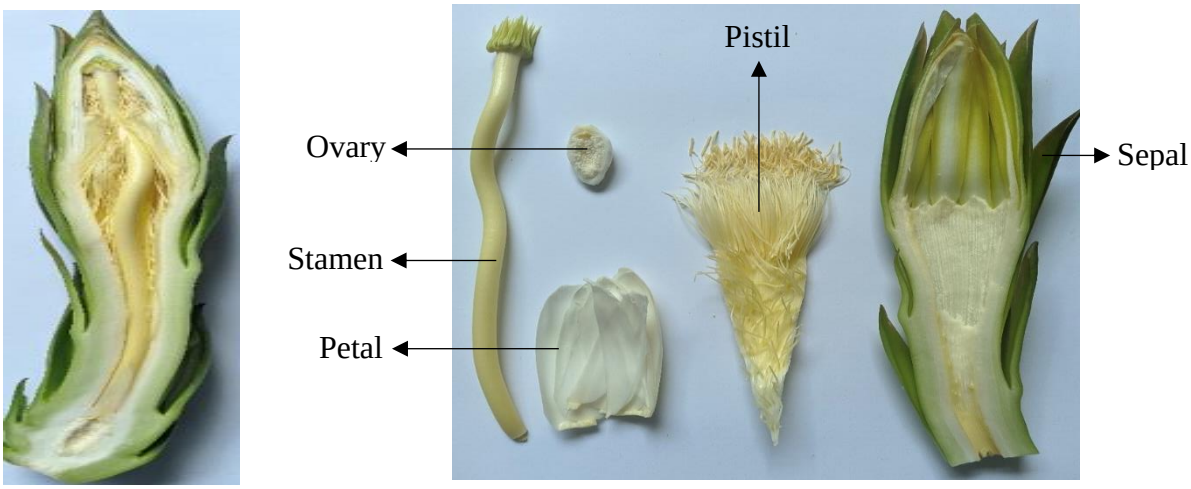

Figure 2. Parts of *Hylocereus undatus* flowers at the stage of 2-3 days before blooming

H. undatus flowers (HUF) at different periods of flowering (**Figure 1**) were dried, ground to powder. For the first step, HUF1-4 were extracted with 96% or 70% ethanol (Chemsol company, Vietnam) (noticed as A, B) under hot maceration protocol (1 g powder: 20 mL ethanol); combined liquids were clarified by filtration, then concentrated to dryness. Eight HUF extracts (HUF1A, HUF2A, HUF3A, HUF4A, HUF1B, HUF2B, HUF3B, and HUF4B) were screened for *in vitro* tyrosinase inhibitory activity to select potential collecting time (2 - 3 days before blooming) and solvent (70% ethanol). For the second step, HUF at the potential time were divided into stamen (st), pistil (pi), petal (pe), ovary (ov), and sepal (se) (**Figure 2**); dried, ground to powder, and extracted with 70% ethanol under hot maceration protocol (1 g powder: 20 mL ethanol), then concentrated to dryness.

2.4. Phytochemical study

Preliminary phytochemical screening by thin-layer chromatography [11]

The HUF extracts were completely dissolved in methanol at the concentration of 1 mg/mL. These solutions (8 µl) were applied to TLC using *silica gel* F254 (Merck, Germany) as the coating substance and dichloromethane - methanol (95:5) or chloroform-methanol-H_2O (65:35:10) (Chemsol Company, Vietnam) as the developing solvent. Once the top of the solvent rises to about 5 - 10 cm from the origin, dry in air. The sample spots were observed under a UV lamp 254 nm, 365 nm and by spraying with VS reagent (1% vanillin/ethanol + 10% H_2SO_4/ethanol) followed by heating at 105ºC. The spots in the chromatogram obtained from the sample solution were calculated the R_f value (the ratio of distance traveled by the compound and distance traveled by the solvent front).

Identification of triterpenoid compounds [11]

The triterpenoid compounds in HUF extracts were identified by Liebermann - Burchard reaction. The HUF extracts were thoroughly dissolved in the mixed solvent of chloroform and acetic anhydride (Chemsol Company, Vietnam) at the concentration of 1 mg/mL in a dry tube. Then concentrated H_2SO_4 (1 mL) was added slowly into the tube wall. The reaction is positive when the interface layer between two solvents turns reddish-brown.

2.5. Evaluation of *in vitro* tyrosinase inhibitory activity by Dopachrome assay

The tyrosinase inhibitory activity was evaluated according to the method described previously by Batubara *et al.* (2010) using L-tyrosine substrate with modifications [12]. The HUF extracts were prepared in 1% dimethyl sulfoxide (DMSO) in phosphate buffer solution (50 mM PBS pH 6.5) at different concentrations (50 – 1000 µg/mL). 70 µL of each concentration were mixed with 30 µL enzyme tyrosinase 333 U/mL (prepared in PBS) in a 96-well plate. After pre-incubation for 10 min at 25 °C, 100 µL of L-tyrosine (2 mM prepared in PBS) were added to each well. The reaction mixture was incubated for 24 min at 25°C. The absorbance was measured at 490 nm to determine the dopachrome amount. Kojic acid was prepared in water at the concentrations of 50, 25, 12.5, 6.25, and 3.125 µg/mL used as positive control while DMSO 1% in PBS was used as a negative control. A blank was prepared by adding sample solution to the reaction mixture without the enzyme. Each sample was tested in triplicate. The tyrosinase inhibitory activity was calculated according to the following equation:

$$\text{Inhibition (\%)} = [1 - (OD_{sample} - OD_{blank\ (sample)})/(OD_{negative\ control} - OD_{blank\ (negative\ control)})] \times 100$$

DMSO, fungal tyrosinase (T3824-25KU), L- Tyrosine BioUltra (93829-25G), and kojic acid (K3125-5G) were purchased from Sigma-Aldrich, USA.

3. RESULTS

3.1. Morphological characteristics *H. undatus* flower

The *H. undatus* flower lifespan (from bud formation to blooming) is about 18 - 21 days. The flowers are 25 - 30 cm long, 15 - 17 cm wide, scented, and hermaphroditic. They are bell-shaped, tubular with a crown of long green scaly sepals arranged in a spiral and several thin white petals. The sepals and petals are combined to form a tube. The flower buds 5 - 6 days old (HUF1) begin to form the ovules; the stamens from anthers with few pollen grains. The flowers 8 - 15 days old (HUF2) have a style and a stigma as well as form the ovary body; the anthers have many pollen grains; the cream-colored lobed stigmas and stamens arrange spirally on the perianth.

The flower with anthesis is at the stage of 2 - 3 days before blooming or 16 - 19 days old (HUF3). After pollination (HUF4), the flower begins to wilt.

3.2. Preparation of ethanolic extracts from *H. undatus* flowers

The obtained HUF extracts were a dark brown color, bitter taste, and characteristic aroma of medicinal herbs. The result of the preparation of extracts from 10 grams of each HUF powder was presented in **Table 1**. With the same solvent (96% or 70% ethanol), the extraction yield of HUF at four different periods of flowering decreased gradually in the order: 2 > 3 ~ 1 > 4. For HUF at each flowering period, the extraction yield with 70% ethanol was higher than that with 90% ethanol (about 3 folds). The extraction yield with 70% ethanol from five parts of HUF 2-3 days before blooming was not significantly different.

Table 1. Extraction yield (%) of ethanolic extracts from HUF flower

Extract	Weight (g)	Extraction yield (%)	Extract	Weight (g)	Extraction yield (%)
HUF1A	0.7083	7.08	**HUF-pi**	2.8600	28.29
HUF2A	1.1016	11.02	**HUF-st**	2.7657	27.96
HUF3A	0.9557	9.56	**HUF-pe**	3.3589	33.71
HUF4A	0.4485	4.49	**HUF-ov**	2.4705	25.27
HUF1B	2.5836	25.84	**HUF-se**	2.5540	26. 07
HUF2B	3.5590	35.59			
HUF3B	2.3662	23.66			
HUF4B	1.3946	13.95			

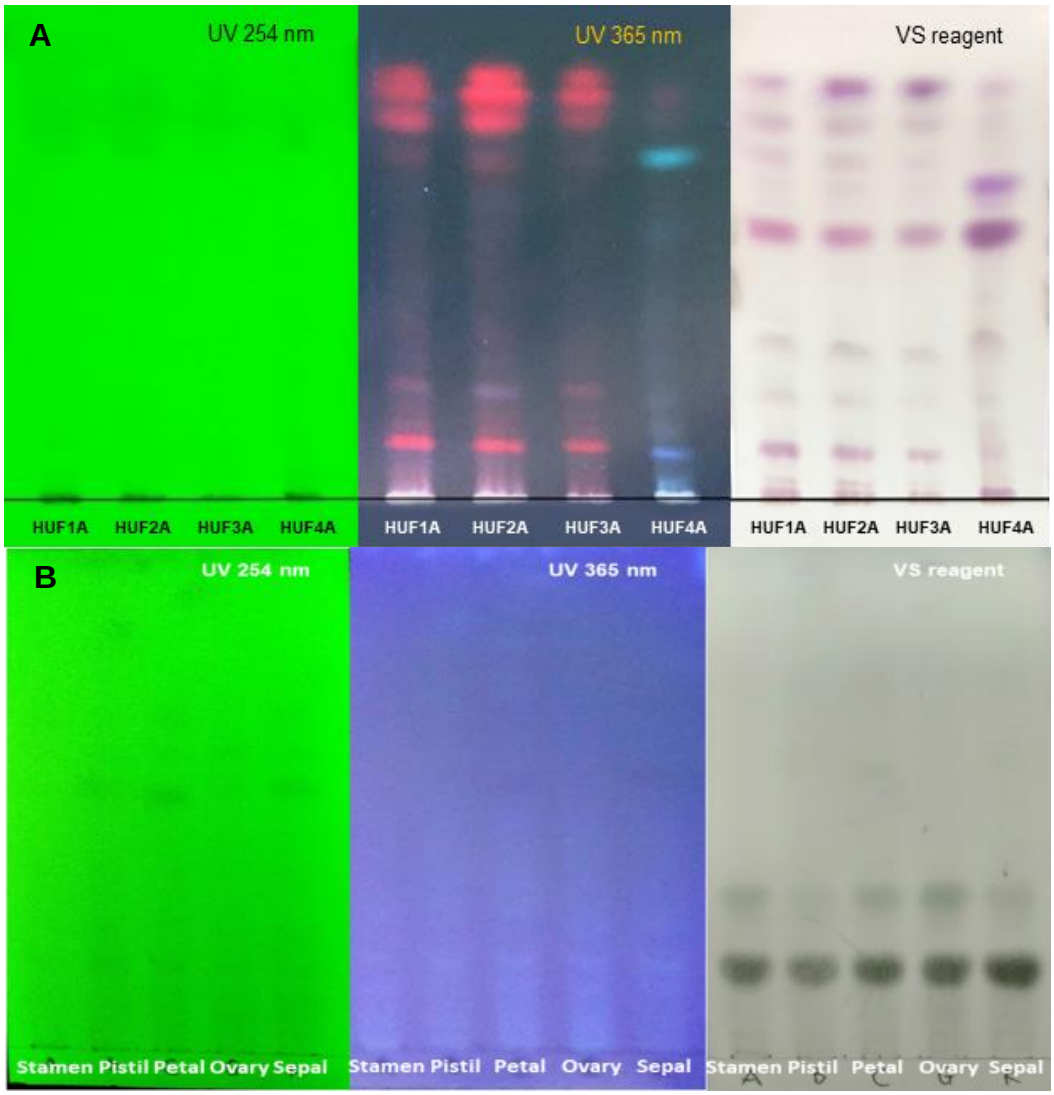

Figure 3. The chromatogram of ethanolic extracts from *H. undatus* flowers harvested at the four flowering stages using mobile phase of dichloromethan - methanol (95:5) (A) and from five different parts of *H. undatus* flowers using mobile phase of chloroform - methanol - H_2O (65:35:10)

3.3. Phytochemical characteristics

The results of preliminary phytochemical screening *via* TLC (**Figure 3A**) with solvent system dichloromethane - methanol (95:5) showed that the HUF1, HUF2, HUF3 extracts contained a lot of chlorophyll because of the presence of many sepals. TLC showed the differences in the main compounds of HUF4 compared to the three other HUF extracts. The main spots in the chromatogram appear purple with VS reagent indicated that triterpenoids are present in the HUF extracts.

The TLC analysis with solvent system chloroform-methanol-H_2O (65:35:10) (**Figure 3B**) showed that five different parts of *H. undatus* flowers have similar chemical compositions with similar main spots in the chromatogram with VS reagent. The result of analysis by TLC corresponded to the positive result of identification of triterpenoid *via* Liebermann - Burchard reaction (**Figure 4**), in which, the HUF3-ov, HUF3-se exhibited the darker color than HUF3-pe, HUF3-st, and HUF3-pi.

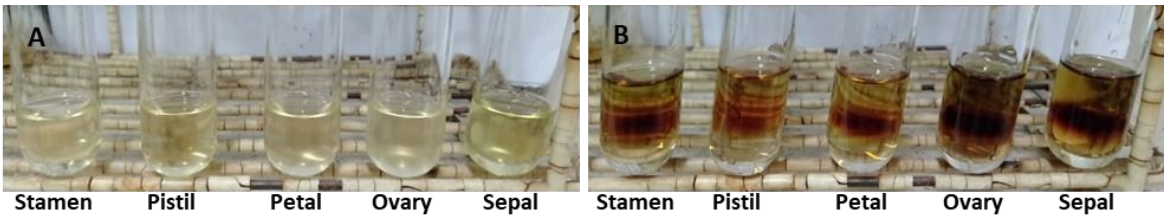

Figure 4. Image of Liebermann - Burchard reaction with ethanolic extracts from five different parts of *H. undatus* flowers: (A) Extracts diluted in acetic anhydride; (B) Extracts diluted in acetic anhydride + H_2SO_4 98%

Table 2. *In vitro* tyrosinase inhibition percentage (TI - %) of ethanolic extracts from *H. undatus* flowers harvested at the four flowering stages at the concentration of 1 mg/mL

Extract	Tyrosinase inhibition percentage (%)	Extract	Tyrosinase inhibition percentage (%)
HUF1A	**111.79 ± 1.54**	HUF1B	**99.70 ± 1.14**
HUF2A	**120.47 ± 0.26**	HUF2B	**99.40 ± 0.15**
HUF3A	35.13 ± 0.35	HUF3B	**98.78 ± 3.12**
HUF4A	37.69 ± 3.09	HUF4B	1.15 ± 0.71

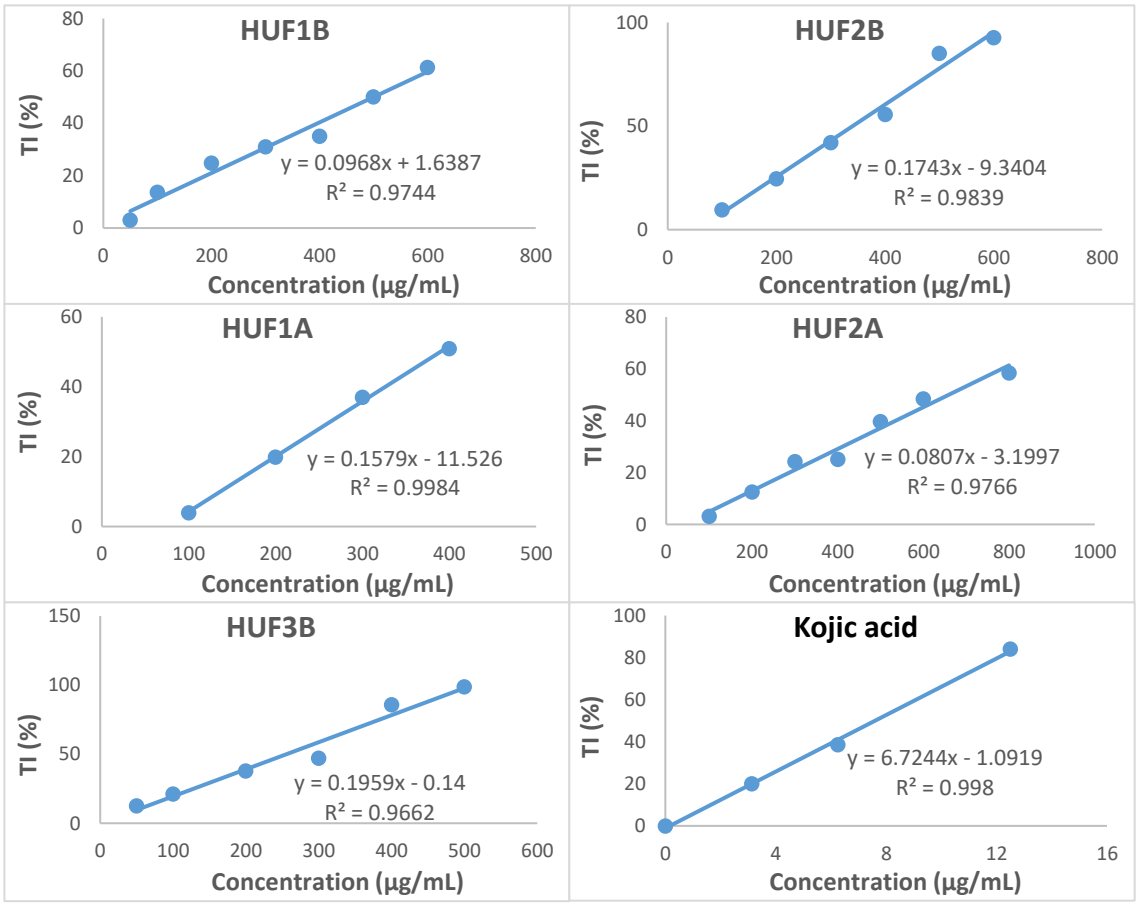

Figure 5. *In vitro* tyrosinase inhibition percentage (TI - %) of ethanolic extracts from *H. undatus* flowers harvested at the four flowering stages and kojic acid

3.4. *In vitro* tyrosinase inhibitory activity

As shown in **Table 2**, five HUF extracts (HUF1A, 2A, 1B, 2B, 3B) showed *in vitro* tyrosinase inhibitory activity with an inhibition percentage of about 100% at the concentration of 1 mg/mL. Therefore, these five extracts were evaluated *in vitro* tyrosinase inhibitory activity at the different concentrations to determine their IC_{50} value compared to that of kojic acid as the positive control.

Based on IC_{50} which were calculated from the linear regression of sample concentration and *in vitro* tyrosinase inhibition percentage (**Figure 5**), the following order of tyrosinase inhibition was observed for five HUF extracts: **HUF3B (266.40 µg/ml)** > HUF2B (373.81 µg/ml) > HUF1A (397.67 µg/ml) > W1B (478.00 µg/ml) > W2A (692.88 µg/ml). The HUF3B extract was the most potent inhibitor of tyrosinase with IC_{50} value of 266.4 µg/ml (35-fold higher than IC_{50} of 7.60 µg/ml of kojic acid).

Table 3. *In vitro* tyrosinase inhibition percentage (TI - %) of 70% ethanol extracts from five different parts of *H. undatus* flowers at the tested concentrations

Concentration (µg/mL)	HUF extract				
	HUF3-pi	**HUF3-st**	**HUF3-pe**	**HUF3-ov**	**HUF3-se**
1000	16.99 ± 2.05	16.41 ± 1.41	18.40 ± 2.85	24.91 ± 3.60	25.93 ± 3.65
750	16.75 ± 3.34	14.60 ± 0.33	16.18 ± 0.68	26.98 ± 0.92	21.09 ± 2.74
500	20.20 ± 2.28	12.27 ± 0.96	18.21 ± 2.73	20.32 ± 1.19	17.84 ± 2.78
200	14.35 ± 1.98	6.77 ± 0.96	8.98 ± 1.72	9.30 ± 0.45	7.00 ± 0.49
100	13.38 ± 4.69	4.89 ± 0.59	7.08 ± 1.18	9.97 ± 2.23	4.62 ± 1.45
50	7.50 ± 0.32	6.07 ± 0.45	4.43 ± 0.93	2.55 ± 1.20	2.47 ± 1.91

Table 3 showed that the ethanolic extracts from five separated parts of *H. undatus* flowers exhibited weak *in vitro* inhibitory activity on the tyrosinase enzyme. At the concentration of 1000 µg/mL, their inhibition percentage was from 16.41% to 25.93%. Primarily, *in vitro* tyrosinase inhibitory activity of HUF3-ov, HUF3-se, HUF3-pe extracts seemed higher than that of the other two extracts (HUF3-pi and HUF3-st); however, this difference was insignificant.

4. DISCUSSION

Tyrosinase is a crucial enzyme in synthesizing melanin through melanogenesis; tyrosinase inhibitors have been widely used as cosmetics or skin lightening agents. The medicinal plants exhibited inhibitory tyrosinase activity, and fewer adverse effects have been observed in cosmeceutical research.

The present study provided the floral morphology at the different stages of *H. undatus* flowers collected from Binh Thuan Province, Vietnam. The observations correspond to those described previously [2]. There are differences in the formation and maturation of the sepal, petal, stamen, ovary, pistil between four periods of *H. undatus* flowering; hence, this could be responsible for the phytochemical difference and for a strong decrease in *in vitro* inhibitory tyrosinase activity of ethanolic extracts from *H. undatus* flowers at stage 2 - 3 days after blooming.

In fact, in terms of the preparation of ethanolic extracts, the extraction yield from *H. undatus* flowers at stage 2 - 3 days after blooming was the lowest: 2 - 3 folds lower than that from the flower at three other stages. In addition, the analysis of chemical constituents of extracts by TLC also showed the difference between *H. undatus* in three early stages (HUF1-3) and the latter stage (HUF-4). Ethanolic extracts of HUF1-3 had similar red-pink main spots under UV365 nm while these spots were absent in HUF4 extract; however, with VS reagent HUF4 extract had more dark purple spots indicated that the triterpenoid compounds appear differently between the first 3 stages before blooming and the period after pollination. Thereby, there is a possible relationship between the phytochemical constituents in general as well as the triterpenoid compounds of HUF4 extracts and *in vitro* inhibitory tyrosinase activity.

According to Ly Kieu Huong and Tran Thi Van Anh (2020), the raw materials of *H. undatus* flowers at stage 2 - 3 days after blooming have triterpenoid compounds, flavonoids, coumarins, anthraglycosides, tannins, saponins, reducing agents, and polyuronic compounds [10]. Some triterpenoid compounds were isolated in *H. undatus* flower such as chalinasterol, ergost 4,24(28) dien-3-one [10]. Another study from Chinese researchers showed that flavonoids were the main active compositions in *H. undatus* flower [13, 15, 16]. This suggested that besides the triterpenoid constituents, flavonoids could play an important role in the inhibitory tyrosinase activity of *H. undatus* flower. This suggestion corresponded to the obtained results. Compared to 96% ethanol, 70% ethanol had a higher extraction yield and obtained extracts exhibited *in vitro* inhibitory tyrosinase activity stronger, especially for HUF3 extracts. In the theory, 70% ethanol is a recommended solvent for the extraction of flavonoids from herbal plants. The HUF3B extract exhibited *in vitro* inhibitory tyrosinase activity strongest; this indicated that complete formation and maturation of all flower parts at stage 2 - 3 days before blooming could be responsible for strong bioactivities of *H. undatus* flower.

At the onset of flowering, 3 - 5 spherical buttons emerge from the stem margins and 2 - 3 of these may develop into flower buds. According to Castillo *et al*. (2005) reported that one of the problems of *H. undatus* is the reduced number of well-developed concerning the total number of produced flowers [14]. So, the flower thinning could be used to increase the fruiting yield. The obtained results indicated that the flower thinning could be carried out on days 16 - 19 (corresponding to the period 2 - 3 days before blooming) to collect the flower with high bioactivity.

Some Chinese studies showed *in vitro* antioxidant activity of *H. undatus* flowers in the order: ovary > petal ~ whole flower > pistil ~ sepal ~ stamen [8, 13] while *in vitro* inhibitory tyrosinase activity in the order: stamen > petal ~ sepal [9]. These results suggest the flower parts contribute differently to the flower's bioactivity; thus, the perianth flower (petal and sepal is often rejected after pollination)

could be collected and exploited their bioactivity to limit environmental pollution due to their degradation. In this study, the triterpenoids were found as the main constituents *H. undatus* flowers and 70% ethanol extracts from five different parts of *H. undatus* flowers were evaluated *in vitro* inhibitory tyrosinase activity. The result showed that *in vitro* inhibitory tyrosinase activity of each flower part is related to the triterpenoid constituents. The obtained results showed that *in vitro* tyrosinase inhibitory activity of petal and sepal extracts was higher than that of stamen; this did not correspond to the report about *in vitro* tyrosinase inhibitory activity of Chinese *H. undatus* flowers [9]. This difference could be explained by the differences in geographical origin and chemical composition. The triterpenoids were found as the main constituents in *H. undatus* flowers harvested from Binh Thuan Province, Vietnam [10] while Chinese *H. undatus* flowers have been reported as the main compositions of flavonoids [15, 16].

The strengths of this study lie in being the first study to evaluate the triterpenoid constituents and *in vitro* tyrosinase inhibitory activity of *H. undatus* whole flowers at four different periods of flowering compared to those of each separated part (stamen, pistil, petal, ovary, and sepal). The present study suggests that there could be a synergistic effect in tyrosinase inhibitory activity of flower parts because of the differences in the chemical constituents. Thus, it is not necessary to classify the part of *H. undatus* flower if using it as the material for medicinal purposes. The inhibitory tyrosinase activity of 70% extract from *H. undatus* suggested the application in browning-prevention agents for food or as skin-whitening materials for cosmetics. However, the limitation of this study is that the chemical analysis only focused on triterpenoid constituents and *in vitro* tyrosinase inhibitory activity of *H. undatus* flowers from Binh Thuan Province. In addition, the present study has not determined the differences in chemical compounds and biological activities between several species of genus *Hylocereus* including two species *H. polyrhizus* and *H. undatus* popularly cultivated in Vietnam, between different parts (stems, flowers, peels, and pulps) as well as between different agricultural areas. Thereby, further studies should be carried out to analyze the chemical constituents of all the different parts of *H. undatus* (stems, flowers, peels, and pulps) and to fully access the contribution of different chemical constituents for the bioactivity. The obtained results will provide scientific evidence for the wide application of these raw materials in the pharmaceutical and cosmetic industries.

Conclusion

The present study provided information about the morphological characteristics at the different flowering stages of *H. undatus* flower collected from Binh Thuan Province, Vietnam. The results showed that their ethanolic extracts from *H. undatus* flower contain triterpenoid compounds. The 70% ethanol extract from whole *H. undatus* flower at the stage of 2 - 3 days before blooming exhibited strong tyrosinase inhibitory activity. This result suggested the application of *H. undatus* flowers as browning-prevention agents for food or as skin-whitening materials for cosmetics.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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