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Collagenase and Tyrosinase Inhibitory Activities and Stability of Facial Cream Formulation Containing Cashew Leaf Extract

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Abstract: The cashew tree (*Anacardium occidentale* L.) is a tropical plant found widely in many Southeast Asian countries, including Thailand, and contains bioactive phenolic compounds with antioxidant activity. The natural antioxidants such as collagenase and tyrosinase inhibitors found in medicinal plants are promising agents in cosmetic products. This study evaluated the inhibitory activities of the collagenase and tyrosinase from cashew leaf extracts by developing and evaluating the stability of facial cream formulations. The ethanol (DEN), ethyl acetate (DEA) and distilled water (DDW) crude extracts of cashew leaves were investigated for their bioactive compound efficacy. The DDW extract had the highest yield (24.97%). All the extracts were investigated for their antioxidant activities. The DEN extract showed the highest DPPH radical-scavenging ability, ferric-reducing power and flavonoid compounds, which were 152.04 ± 2.40 mg gallic acid/g extract, 37.90 ± 1.07 mg gallic acid/g dry weight and 7.63 ± 0.07 mg quercetin/g dry weight, respectively. The DDW extract exhibited the highest potent activity, which was 111.00 ± 0.78 mg gallic acid/g dry weight in terms of phenolic content, while the DEN extract showed the highest tyrosinase inhibition at 0.100 mg/mL (46.97 ± 3.34%) and collagenase activity at 40 µg/mL. The results suggested that the ethanolic extracts from cashew leaves showed promise for use in skincare product development. Cosmeceutical formulations for skincare were prepared. The formula mixed with DEN extract and added to whitening and anti-aging skincare cream demonstrated good stability and physical properties.

Keywords: cashew; collagenase activity; tyrosinase activity; antioxidant; anti-aging; plant extract

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1. Introduction

The cashew tree (*Anacardium occidentale* L.) belongs to the Anacardiaceae family. This tropical plant is widely distributed in many areas of southeast Asia and tropical America, especially in northeastern Brazil. Both the nut (fruit) and the cashew apples or pseudo-fruits of the cashew tree are marketed, and it is rich in fructose, glucose and amino acids and has a good antioxidant content and is high in ascorbic acid and phenol compounds [1,2]. Cashew apples are used as healthy alternatives to functional foods, while the leaf, stem and bark extracts are used in traditional medicines to treat inflammation, diarrhea, rheumatic diseases, hypertension and infectious diseases [3–7].

Plants containing phytochemicals are beneficial in human diets as they act as natural antioxidants and have health benefits provided by their polyphenols, alkaloids, flavonoids, saponins, tannins, glycosides, anthraquinones and terpenoids [8,9]. Phytochemicals identified in the extracts of the leaves, bark and root of the cashew tree include flavonoids, polyphenols, alkaloids, saponins, tannins, coumarin, quinone and cardiac glycoside [10–12]. Shukri and Alan [13] found that the most common phenolic compounds found in the leaf

shoots of two varieties of *A. occidentale* were flavonol glycosides, with other major components including kaempferol 3-O-glucoside, kaempferol 3-O-arabinofuranoside, quercetin 3-O-glucoside and quercetin 3-O-galactoside, while Andarwulan et al. [5] reported that quercetin was the dominant flavonoid, and chlorogenic acid was the dominant phenolic acid in cashew leaves. Kaempferol and quercetin are flavonoid compounds found in a variety of plants such as kale, tea and broccoli that act as potent antioxidants [14], indicating the potential bioactivity of plants as antioxidant sources. Costa et al. [15] identified gallic acid, luteolin, epicatechin gallate and agathisflavone in ethanolic extracts of *A. occidentale* bark, which showed a moderate activity against all cancer lines (acute promyelocytic leukemia, human colon cancer, human lung mucoepidermoid carcinoma and mastocytoma) with a low cytotoxicity for murine fibroblasts.

Plants and plant extracts are widely used in cosmetics and for many other purposes such as whitening, moisturizing, sunscreen, anti-wrinkle activity, coloring cosmetics, anti-acne, preservatives, antioxidants and thickeners. Skin-lightening products made from natural plant extracts are now becoming popular as effective, safe and non-toxic products [16]. Antioxidants have been widely incorporated into anti-aging cosmetics due to their free-radical-scavenging activity that helps to reduce or prevent skin oxidative stress and can slow down skin aging [17]. Anti-tyrosinase activity refers to the ability of a compound to inhibit the activity of tyrosinase, an enzyme that is involved in the production of melanin in the skin [18]. Inhibiting tyrosinase can help to reduce the production of melanin, which can be beneficial in the treatment of hyperpigmentation disorders such as age spots, freckles and melisma [19,20]. There are several natural compounds that have been shown to have tyrosinase inhibitory activity. Kojic acid is a natural compound that is produced by several species of fungi such as *Aspergillus flavus* [21], and oxyresveratrol [22] is obtained from plant materials. It has been shown to have a strong tyrosinase inhibitory activity and is often used in skin-lightening products to help reduce hyperpigmentation [23]. Polyphenols such as flavonoids, tocopherols and phenolic acids also have anti-collagenase and anti-elastase activity [24]. Other dominant natural compounds that might contribute to anti-collagenase properties include quercetin, quercetin-3-O-rhamnoside, catechin, epigallocatechin gallate, epicatechin and kaempferol [24,25]. Collagenase is an enzyme that breaks down collagen, a protein that is found in the connective tissue of the skin, bones and other tissues. Collagen makes up 70–80% of the dry weight of skin and is an important component of the skin's structural support, and its degradation can lead to the loss of skin elasticity and the development of wrinkles [24,26].

Numerous investigations on the phytochemistry of cashew extracts have not connected any particular activity to the identified chemicals. Here, the bioactive components of cashew leaf extracts were examined to determine their contents of potential antioxidant, anti-tyrosinase and anti-collagenase agents as natural sources for skincare products.

2. Materials and Methods

2.1. Extract Preparation

Leaves of *A. occidentale* L. were purchased at a local market in Klongtom district of Krabi Province, Thailand. The voucher specimens of the plant samples were authenticated by a botanist and deposited at the School of Pharmaceutical Sciences, University of Phayao, Thailand. The reddish young leaves were rinsed several times with tap water, cut into small pieces and dried in a hot-air oven at 50 °C. The dried leaves (200 g) were ground into a powder before extraction in either 95% ethanol (DEN) or ethyl acetate (DEA) at room temperature for 72 h, while the other dried leaves were soaked in warm distilled water for 3 h (DDW). The samples were filtered and evaporated using a vacuum rotary evaporator, and the percentage yield of each extract was calculated. The extracts were kept in amber bottles and stored at 4 °C until further use.

2.2. Determination of Total Phenolic Content

The total phenolic content of the extracts was determined using the Folin–Ciocalteu test, following Mungmai et al. [27] and Chandler and Dodds [28] with slight modifications. The extracts (250 µL) were mixed with 1250 µL of deionized water. Then, 95% ethanol (250 µL) and 50% Folin–Ciocalteu reagent (125 µL) were added to the mixture. The mixture was shaken and allowed to stand at room temperature for 5 min before adding 250 µL of 5% Na_2CO_3. After incubation in the dark at room temperature for 60 min, the absorbance of the mixture was measured at 725 nm using a UV–Vis spectrophotometer. The total phenolic content was expressed as gallic-acid-equivalent (GAE) in mg/g dry extract (mg GAE/g extract).

2.3. Determination of Total Flavonoid Content

Flavonoid compounds were determined using a aluminum chloride colorimetric assay [29]. Extracts (250 µL) were mixed with 50 µL of 10% $AlCl_3$ and 750 µL of methanol. Then, 50 µL of 1M potassium acetate and 1400 µL of deionized water were added to the mixture. The mixture was shaken and incubated for 30 min in the dark at room temperature. The absorbance of the mixture was measured at 415 nm using a UV–Vis spectrophotometer. The total flavonoid content was expressed as quercetin-equivalent (QE) in mg/g dry extract (mg QE/g extract).

2.4. 2,2-Diphenyl-1-picrylhydrazyl (DPPH) Radical-Scavenging-Capacity Assay

The 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical-scavenging activity of the extracts was measured according to the modified method of Duen et al. [30]. In brief, different dilutions of extracts (80 µL) were mixed with 67 µL of 1 M Tris-HCl (pH 7.9) and 130 µM of DPPH in methanol. The mixture was shaken and incubated for 20 min in the dark at room temperature, and the absorbance was measured at 517 nm using a UV–Vis spectrophotometer. Results were expressed as gallic-acid-equivalent of antioxidant (GAE) in mg/g of dried extract (mg GAE/g extract).

2.5. Ferric-Reducing Antioxidant Power (FRAP) Assay

The ferric-reducing antioxidant power of the extracts was determined following the method described by Oyaizu, [31] with slight modifications. Different extract dilutions (120 µL) were mixed with 290 µL of 0.2 M phosphate buffer (pH 6.6) and 290 µL of 1% (*w*/*v*) potassium ferricyanide followed by incubating in a water bath at 50 °C for 20 min. Subsequently, 290 µL of 10% (*w*/*v*) trichloroacetic acid was added to the mixture and centrifuged at 3000 rpm for 10 min. The supernatant (1000 µL) was diluted with 1000 µL of deionized water and 400 µL of 0.1% (*w*/*v*) of $FeCl_3$ was added. The mixture was shaken thoroughly, and the absorbance was measured at 700 nm using a UV–Vis spectrophotometer. Results were calculated as percentage of inhibition and expressed as mg GAE/g of extract.

2.6. Determination of Tyrosinase-Inhibition Activity

Tyrosinase inhibition activity was determined using the dopachrome method described by Masuda et al. [32] with slight modifications. The extracts were diluted with 50% (*w*/*w*) dimethyl sulfoxide. Tyrosinase reactions were performed in a 96-well plate, with each well containing 40 µL of extracts at different dilutions, and 140 µL of 0.1 M phosphate buffer (pH 6.6) followed by 40 µL of tyrosinase solution (31 U/mL). After incubation for 10 min, 40 µL of 2.5 mM L-DOPA was added to the mixture. The 96-well plate was allowed to stand for 10 min at room temperature, and the absorbance of the solution was measured at 475 nm using a microplate reader. Each sample was accompanied by a blank. All the components, except L-DOPA, used kojic acid as the reference substance.

2.7. Determination of Collagenase Inhibition Activity

Collagenase activity was investigated using fluorescein-conjugated gelation as the substrate following Zinger et al. [33] with some modifications. The enzyme solution was

added to the substrate solution followed by a reaction buffer (0.5 M Tris-HCl, 1.5 M NaCl, 50 mM $CaCl_2$, 2 mM NaN_3, pH 7.6). The fluorescence intensity of each sample was measured every 2 min for 20 min using a multimode reader with excitation set at 485 nm and emission at 530 nm. Collagenase concentration was calculated using a calibration curve generated by collagenase samples of known concentrations.

2.8. Formulation of Facial Cream

The facial cream base formulation was prepared from various compositions by a cool process. Deionized water, polyacrylamide, C13-C14 isoparafin, laureth-7, dimethicone, propylene glycol and phenoxyethanol were mixed together. These were then homogenized until a homogeneous emulsion was obtained. The spreadability, feel-on-skin and pH of the cream base was determined. The stability of the cream base was tested by centrifugation at a speed of 3500 rpm for 30 min. The stable cream base was then incorporate with cashew leaf extract and compared with facial cream without extract addition.

2.9. Stability Studies

Stability studies were performed under various conditions at room temperature, 4 °C and 45 °C for 3 months and using 6 cycles of the heating/cooling method (45 °C, 48 h alternated with 4 °C, 48 h for 1 cycle). Organoleptic characteristics as the color, odor, phase separation, homogeneity, feel-on-skin, pH and viscosity of the creams were evaluated [34].

2.10. Statistical Analysis

Results were expressed as mean values ± standard deviation (SD) using SPSS version 17 for Windows. Significant differences between the groups were determined using one-way ANOVA followed by Tukey's post hoc test, with the level of significant difference considered at $p < 0.05$.

3. Results and Discussion

3.1. Percentage Yield of Cashew Leaves

The cashew leaves were extracted using ethanol (DEN), ethyl acetate (DEA) and distilled water (DDW). The DDW extract presented the highest percentage yield at 24.97%, while the percentage yields of DEN and DEA were 22.76% and 1.82%, respectively. The difference in yields depended on the solvent with varying polarity, extraction temperature, extraction time and phytochemicals in the plants or parts of the plants [35,36]. The results indicated that the major phytochemicals in the cashew leaves were high in polarity and soluble in water. The most common phenolic compounds found in the cashew leaves were flavonol glycosides consisting of major components such as kaempferol 3-O-glucoside, kaempferol 3-O-arabinofuranoside, quercetin 3-O-glucoside, quercetin 3-O-galactoside and chlorogenic acid, while quercetin was the dominant flavonoid [5,13]. Pin et al. [37] found that an aqueous leaf extract of betel (*Piper betel*) gave the highest percentage yield, while Markom et al. [38] determined that *Phyllanthus niruri* extract recorded the highest percentage yield from water and reported that polar compounds were more easily extracted than non-polar compounds.

3.2. Total Phenolic Content, Flavonoid Content and Antioxidant Activity

The total phenolic content, total flavonoid content and antioxidant activities of the cashew leaf extracts are presented in Table 1. The DDW extract had the highest total phenolic content that was statistically significant ($p < 0.05$), which was 111.00 ± 0.78 mg GAE/g extract compared with the standard gallic acid, while the DEN extract had the highest total flavonoid content that was statistically significant ($p < 0.05$), which was 7.63 ± 0.07 mg QE/g extract compared with the quercetin standard. The total phenolic content was dependent on the solvent used in the extraction and its polarity. Phenolic compounds are usually mainly responsible for the antioxidant properties of plants, and most of these compounds are classified as hydrophilic antioxidants [39]. The antioxidant

activity of phenolics is related to the number and position of the hydroxyl groups in their aromatic rings; therefore, phenolic compounds have an important influence on the antioxidant activity of plant extracts [40]. Phenolic and flavonoid compounds are widely found as secondary metabolites in plants. Both phenolic and flavonoid compounds directly promote antioxidative action, facilitating the prevention of damage to cells caused by free radicals [41]. In addition, they have been shown to have potential health benefits, including anti-bacterial and anti-inflammatory effects, the ability to protect skin from UV radiation and anti-carcinogenic properties [42,43]. They have been the subject of much research for their potential use in the prevention and treatment of a variety of diseases, including cancer, cardiovascular disease and neurodegenerative disorders.

Table 1. Total phenolic content, total flavonoid content and antioxidant activities of cashew leaf extracts (mean ± standard deviation, n = 3).

Test Material	Total Phenolic Content (mg GAE/g Extract)	Total Flavonoid Content (mg QE/g Extract)	DPPH Assay (mg GAE/g Extract)	Reducing Power Assay (mg GAE/g Extract)
DEN	41.39 ± 1.47 ^{b}	7.63 ± 0.07 ^{a}	152.04 ± 2.40 ^{a}	37.90 ± 1.07 ^{a}
DEA	0.91 ± 0.03 ^{c}	0.32 ± 0.06 ^{c}	31.43 ± 1.52 ^{c}	0.53 ± 0.03 ^{c}
DDW	111.00 ± 0.78 ^{a}	3.88 ± 0.03 ^{b}	144.21 ± 3.68 ^{b}	35.59 ± 0.66 ^{b}

Different letters (a, b, c) in the same column indicate significant differences ($p < 0.05$).

The DEN extract showed a significantly ($p < 0.05$) higher DPPH free-radical-scavenging activity than the DDW and DEA extracts, which was 152.04 ± 2.40, 144.21 ± 3.68 and 31.43 ± 1.52 mg GAE/g extract, respectively. This result concurred with Jaiswal et al. [44] who reported that the ethanol-extracted leaf extracts of *A. occidentale* possessed the strongest activity, followed by aqueous- and petroleum-ether-extracted extracts. The reducing power of the extracts, reflecting their antioxidant activity, was determined using a modified Fe^{3+} to Fe^{2+} reduction assay. The results showed that the DEN extract also demonstrated a significantly ($p < 0.05$) higher activity than the DDW and DEA extracts. This study provided useful information about the antioxidant capacity of cashew leaf extracts as important active ingredients for cosmetic products.

3.3. Tyrosinase Inhibition Activity

Tyrosinase is an enzyme that catalyzes the production of melanin in the skin and hair bulbs and in the eyes of animals. Extracts from natural compounds have shown that the activity of tyrosinase inhibitors could be used for hyperpigmentation and in interests for cosmetic applications such as skin whitening. The inhibitory effects of the extracts on tyrosinase enzyme activity were determined to evaluate their potential as skin-whitening agents. The percentages of tyrosinase inhibition activities at 0.1 mg/mL were 65.66 ± 7.06 (kojic acid), 46.97 ± 3.34 (DEN), 32.29 ± 5.75 (DEA) and 32.68 ± 2.66 (DDW) (Figure 1), with IC_{50} values of 0.111 ± 0.010, 0.183 ± 0.024, and 0.158 ± 0.018 mg/mL, respectively. Şöhretoğlu et al. [45] investigated the tyrosinase inhibition potential of some structurally related flavonoids and found that quercetin exhibited the strongest effect. Kishore et al. [46] described twelve flavonoid glycosides from the methanol extract of *Myrsine africana* (Myrsinaceae). Among the list of these compounds, rutin and myricetin-3-O-α-L-rhamnopyranoside showed significant tyrosinase inhibitory effects with IC_{50} values of 0.13 ± 0.003 and 0.12 ± 0.002 mM, respectively, compared to kojic acid (0.01 ± 0.001 mM). In this research, the ethanol cashew leaf extract had a higher flavonoid content than the water extract. The compounds from the various parts of cashew fruits, namely anacardic acids, 2-methyl cardols, cardol triene and cardols, exhibited tyrosinase inhibitory activity [47–49], while the phenolic components 6-[8 (Z), 11 (Z), 14-pentadecatrienyl] salicylic acid and 5-[8 (Z), 11 (Z), 14-pentadecatrienyl] resorcinol exhibited a characteristic competitive inhibition of L-DOPA oxidation [47].

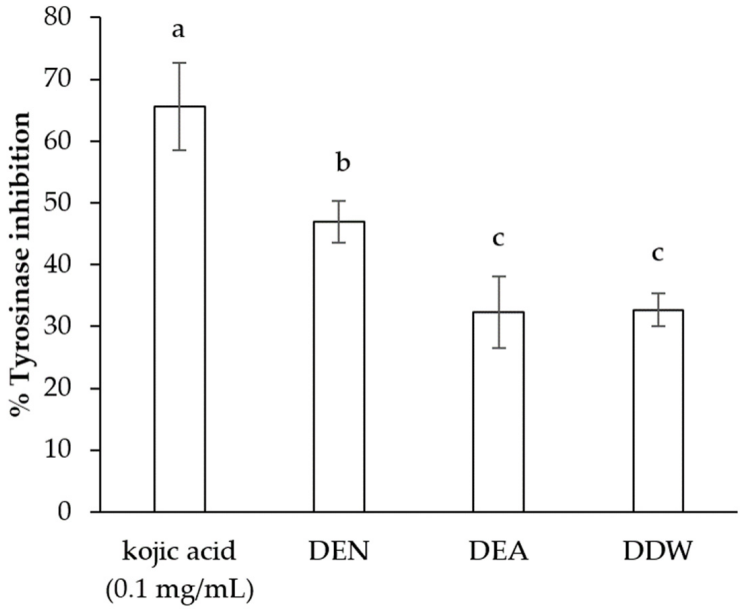

Figure 1. Tyrosinase inhibition of cashew leaf extract (0.1mg/mL) compared with the control (kojic acid). Values are reported as mean ± standard deviation. Different letters (a, b, c) indicate significant differences ($p < 0.05$).

3.4. Collagenase Inhibition Activity

The collagenase enzyme can degrade collagen. As a result, collagen in the underskin or dermis layer is weakened by this enzyme and shows wrinkles because collagenase plays an important role in the skin's aging process. Incubating DEA, DDW and DEN extracts at concentrations of 100, 200 and 400 µg/mL in the collagenase inhibition test gave collagenase activities of 50.1 ± 3.6, 20.6 ± 2.0 and 2.9 ± 1.1% for the DEA extract, while the DDW and DEN extracts recorded no activity at all the studied concentrations, as shown in Figure 2.

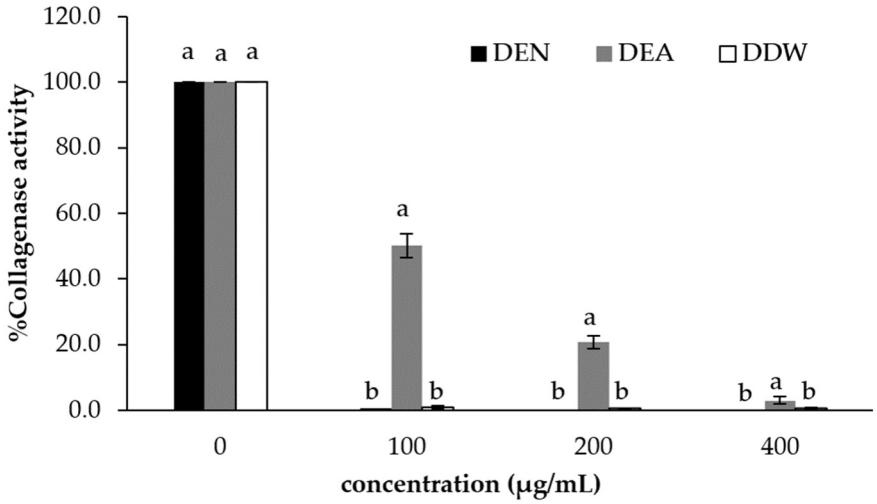

Figure 2. Comparison between cashew leaves extracted with ethanol (DEN), ethyl acetate (DEA) and water (DDW) at concentrations of 100, 200 and 400 µg/mL for collagenase activity. Values are reported as mean ± standard deviation. Different letters (a, b) indicate significant differences ($p < 0.05$).

The results showed that the DDW and DEN extracts at concentrations of 100, 200 and 400 mg/mL inhibited the enzyme's activity. Therefore, the extract concentrations were re-

duced to 10, 20 and 40 µg/mL, as shown in Figure 3. The DEN extract at 40 µg/mL showed the highest inhibition of collagenase activity, which was recorded at zero percent. Fourteen plant extracts in Thailand have been studied for collagenase inhibition, with only two species inhibiting collagenase enzyme, which were *Ardisia elliptica* (IC_{50} = 426.67 µg/mL) and *Annona squamosal* (IC_{50} = 426.67 µg/mL) [50]. According to research by Sin and Kim [51], flavonols have a stronger inhibitory impact on collagenase activity than flavones, isoflavones and flavanones. Therefore, it is thought that the flavonol group of chemicals, including quercetin and kaempferol, which may be found in *A. occidentale*, are what give this plant its strong anti-collagenase activity.

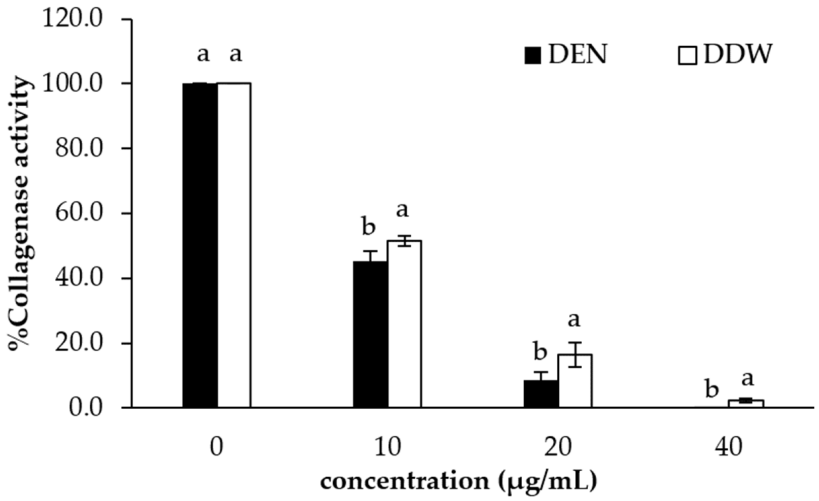

Figure 3. Comparison between cashew leaves extracted with ethanol (DEN), ethyl acetate (DEA) and water (DDW) at concentrations of 10, 20 and 40 µg/mL for collagenase activity. Values are reported as mean ± standard deviation. Different letters (a, b) indicate significant differences ($p < 0.05$).

The cashew leaves extracted with ethanol contained many potent antioxidants, which inhibited the tyrosinase enzyme activity, which can cause dull skin with dark spots, and also inhibited the collagenase enzyme activity, which can lead to sagging skin and wrinkles. Therefore, the cashew leaves extracted with ethanol were suitable for further development as a skincare cosmetic product.

3.5. Stability Test of Facial Cream Products

The physical characteristics of the skin cream formulas were evaluated by testing at room temperature, 4 °C and 45 °C for 3 months and under alternating hot and cold conditions for six heating/cooling cycles. The products were kept at 45 °C for 24 h, alternating with cold conditions (4 °C) for 24 h for one cycle, and the pre- and post-test product changes were evaluated in terms of the texture, color, odor, stratification and acid–base (pH) characteristics of the product. The results showed that the formula was stable with satisfactory physical characteristics under the various storage conditions tested. The physical characteristics such as the basic formula remained the same. The color became darker but did not stratify, and the viscosity changed slightly, while the pH increased at 45 °C (Table 2). The heating/cooling cycle remained within the acceptable limits, and the smell remained the same, signifying that the product was stable.

Table 2. Stability testing results of facial cream containing cashew leaf extracts under various conditions: room temperature (RT), 4 °C and 45 °C for 3 months and six heating/cooling cycles (H/C cycles).

Parameter	Initiation	RT	4 °C	45 °C	H/C Cycle
Viscosity (pas)	1025 ± 3.06	1030.33 ± 4.16	1020.33 ± 13.58	1036.00 ± 5.57	1044.67 ± 10.26
Color	Pale green	Pale green	Pale green	Pale green	Pale green
Homogeneity	Good	Good	Good	Good	Good
Phase separation	No	No	No	No	No
Feel on skin	good	good	good	good	good
pH	6.01	6.12	6.22	6.35	6.56

4. Conclusions

The cashew leaves extracted with ethanol (DEN) showed substantial antioxidant activities and the highest inhibition of the crucial enzymes involved in skin aging such as tyrosinase and collagenase, with the potential for cosmeceutical product development for anti-aging, skin-whitening and antioxidant applications. The facial cream containing cashew leaf extracts was investigated for its stability and physical properties. The results revealed that the stability and physical properties of the facial skin cream were satisfactory under various storage conditions.

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