Oil from Kopyor Coconut for Cosmetic Application

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Submission date: 11-Aug-2022 08:33AM (UTC+0700)
Submission ID: 1881181704
File name: Oil_from_Kopyor_Coconut_for_Cosmetic_Application.pdf (951.62K)
Word count: 5278
Character count: 27940

Industrial Crops & Products 186 (2022) 115221

Contents lists available at ScienceDirect

Industrial Crops & Products

journal homepage: www.elsevier.com/locate/indcrop

Short communication

Oil from *kopyor* coconut (*Cocos nucifera var. Kopyor*) for cosmetic application

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ARTICLE INFO

Keywords:
Kopyor coconut
Macapuno
Coconut oil
Estrogenic
Cosmetic
Lotion

ABSTRACT

Kopyor coconut (KC)[1] (*Cocos nucifera var. Kopyor*) is widely cultivated in Indonesia, Philippines, Malaysia, Sri Lanka, and Thailand. Known as 'Macapuno' coconut in Philipines, the characteristic of this wildtype coconut (WC)[2] mutant variant can be differentiated by its scrambled endosperm. KC oil contains lauric acid and α-tocopherol, which exhibit estrogenic activity and increase skin collagen concentration. Thus, the development of KC oil as a topical cosmetical product is promising. We investigated the estrogenic potential of KC oil from its endosperm and defined the optimum formula for producing a lotion as a pilot for topical cosmetic products. A study of the physical properties of lotion produced from the optimum formula was then performed. The estrogenic activity of KC was determined by MCF-7 cell viability assay using 3-(4,5-Dimethylthiazol-2-yl)− 2,5-Diphenyltetrazolium Bromide (MTT)

1. Introduction

Kopyor coconut (*Cocos nucifera* var *Kopyor*) (KC), known as 'Macapuno', is widely cultivated in Indonesia, Philippines, Malaysia, Sri Lanka, and Thailand (Novarianto et al., 2014). KC is a genetic mutation version of wildtype coconut which affects the endosperms formation and compounds composition compare to the wildtype (Angeles et al., 2018; Mashud and Manaroinsong, 2010; Santoso et al., 1996). KC contains lauric acid (37.93–51 %) as prominent fatty acids components (Angeles et al., 2018; Antu et al., 2020). Studies in rats showed that a 1 % lauric acid diet increased serum estradiol and improved the development of mammary glands (Meng et al., 2017). Though it is not the highest, alfa-tocopherol is one of the beneficial components of KC on estrogen-related activity (Angeles et al., 2018; Santoso et al., 1996). Alfa-tocopherol was reported to stimulate the MCF-7 cell growth, and a high alfa-tocopherol diet increased the expression of estrogen receptor alfa (Bak et al., 2017; Khallouki et al., 2016). Estrogen topical application was reported to increase the collagen concentration on the facial skin. Thus, it improved skin appearance and reduced wrinkled skin (Rzepecki et al., 2019; Silva et al., 2017). Estrogen compounds, including plant-derived estrogen (phytoestrogens) or other estrogenic compounds, effectively overcome the same problem (Dhiani et al., 2015; Jungsukcharoen et al., 2014; Lizcano and Guzmán, 2014).

Thus, we investigated the estrogenic activity of KC oil produced from its endosperm, then applied KC oil to define the optimum formula and developed lotion preparation as a pilot for topical cosmetic products. The estrogenic activity was studied using MCF-7 cell viability assay using MTT method (Tatay et al., 2018). The lotion containing KC oil formula optimization was designed using Design Expert 11.0. Finally, physical properties characterization was performed to the optimum formula of lotion containing KC oil and primary irritation test was conducted in animal model.

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[1] KC: Kopyor coconut
[2] WC: Wildtype coconut

https://doi.org/10.1016/j.indcrop.2022.115221
Received 5 October 2021; Received in revised form 1 June 2022; Accepted 11 June 2022
Available online 21 June 2022

2. Materials and methods

2.1. Materials

2.1.1. Plant material

KC fruit was harvested from Coconut Research Centre (COREC) University Muhammadiyah Purwokerto plantation in Kembaran District, Banyumas Regency, Central Java Province, Indonesia (70 m above sea level) with latitude − 7.414827360293998 and longitude 109.27682766948345. KC used in this research was developed from an embryonic incision technique (Sisunandar et al., 2015) and harvested four months after cultivation. KC meat was separated from the skin and kept in the − 20 °C freezer.

2.1.2. Cell lines

ER[5]-positive breast cancer cell lines MCF-7 were used in the cell viability assay for estrogenic activity determination. The MCF-7 cell line used in the experiments was in passage 8.

2.1.3. Animals

The animals that were used in the primary irritation test were three young adult albino rabbits New Zealand strain. The rabbits were with healthy intact skin and weight not less than 2 kg. The animals were obtained and kept in the animal house facility in Faculty of Pharmacy University Muhammadiyah of Purwokerto. Animal acclimatization were performed seven days prior to the experiments with normal diet and water intake.

2.1.4. Reagents

Reagents for cell culture and cell viability assay: DMEM[6] high glucose (12100046, Gibco), Trypsin-EDTA 0.25%, phenol red (25200056, Gibco), Penicillin-Streptomycin (5000 U/mL) (Pen-strep) (15070063, Gibco), Fetal Bovine Serum (FBS) (F7524, Sigma), Phosphate Buffered Saline (PBS) (in house buffer), MTT (M2128, Sigma), solubilization solution (sodium dodecyl sulphate (SDS) 16% in dimethylformamide (DMF) 40%) (in house solution), 17β-estradiol (E8875, Sigma-Aldrich), Dimethyl sulfoxide (DMSO) (D8418, Sigma).

Reagents and materials used for lotion preparation were all pharmaceutical grades unless otherwise stated. Stearic acid, TEA, cetyl alcohol, lanolin, glycerin, rose oil, nipagin, and nipasol are all purchased from PT. Bratachem, Indonesia.

Reagents for alfa-tocopherol identification and quantification by HPLC method were all analytical grades and purchased from Fisher Scientific.

2.2. Methods

2.2.1. Kopyor coconut oil preparation

KC meat was separated from the skin and kept in the − 20 °C freezer. KC oil was prepared from 1.5 kg of KC meat. The meat was mashed using a food blender (PHILIPS food blender type HR2071/20) before centrifugation to obtain virgin KC oil (Wong and Hartina, 2014). The upper phase (virgin KC oil) was separated from the turbid bottom phase after centrifugation (centrifuge Gemmy type PLC-03) at maximum speed (2422 xg) for 30 min at room temperature (25–30 °C). The KC oil was stored in a dark glass bottle at room temperature prior to use.

2.2.2. MCF-7 cell viability assay

MCF-7 cell viability assay was determined by MTT assay with some modifications (Tatay et al., 2018). MCF-7 cell was cultured in growth media: DMEM supplemented with 10 % FBS and 1 % Pen-strep. After reaching ~80–90% cell confluency, the cells were harvested by adding trypsin. The cells in number ~3 × 10^3 cells/well were cultured in 96-well plates. Growth media were then replaced by free-serum media after 24 h of incubation. KC oil in a serial concentration 100; 80; 40; 20; 10; 5% in DMSO, and estradiol (10^{-3} to 10^{-13} M in DMSO) as the positive control, as well as DMSO (1–10^{-11}%) as solvent control, were added to the cells culture in triplicate for each concentration. Ten microliters of MTT solution (5 mgmL in PBS) were added after three days of incubation. 100 μL of solubilization solution was then added after 4 h of incubation in a CO_2 incubator.

Absorbance measurement at 595 nm wavelength was then performed in the following day. The plates were kept away from the light at room temperature before the measurement. The absorbance data were used to calculate the % cell viability using the following formula:

$$\%\text{cell viability} = \frac{(absorbance\ of\ sample - absorbance\ of\ cell\ control)}{absorbance\ of\ cell\ control} \times 100\%$$

The EC_{50} value was calculated using GraphPad Prism 9.0 based on % cell viability plotted for non-linear regression equation for log (agonist) vs. response – variable slope (four parameters).

2.2.3. Lotion formulation and preparation

The optimum formula for lotion of KC oil was obtained by analyzing the formula design built by Design Expert version 11.0 using the Simplex Lattice Design method. Eight formula design for lotion formula optimization is shown in Table 1.

Lotion was prepared by mixing the oil phase (stearic acid, lanolin, cetyl alcohol, nipasol) and water phase (glycerine and nipagin) after indirect heating for each phase at 65–75 °C. The water phase mixture was added to the oil phase and stirred until it reached homogeneity. TEA and aquadest were added slowly to the mixture and constantly stirred until an emulsion was formed. KC oil and rose oil were then added and mixed well.

Lotions for all optimized design formulas were then characterized its physical properties. Subsequently, all physical properties characteristics were reanalyzed in Design Expert 11.0 to predict the optimum formula.

2.2.4. Physical properties characterization

Physical properties characterization included organoleptic characterization, homogeneity, pH, viscosity, spreadability, stickability, and stability (Iryani et al., 2021).

2.2.5. Primary irritation test

The primary irritation test was conducted following the standard of ISO-10993–10:2010 (Biological evaluation of medical devices, Part 10: Test for irritation and skin sensitization). The ethical clearance of this primary irritation test was granted from the Ethic Committee Faculty of Health Sciences, University Muhammadiyah Purwokerto.

The fur on the backs of the animals were clipped 24 h before treatment to obtain the clean area approximately 10–15 cm. Five sample application sites were defined by marking a dot sign in the four edges on the rabbit skin with area 2.5 × 2.5 cm. These five application sites were

[5] ER: estrogen receptor
[6] DMEM: Dulbecco's Modified Eagle Medium

Table 1
Formula designs for KC oil lotion formula optimization built by Design Expert 11.0.

Components (%)	F1	F2	F3	F4	F5	F6	F7	F8
KC oil	5	5	5	5	5	5	5	5
Stearic acid	6	5	4.5	5.5	4	5	4	6
TEA	2	3	3.5	2.5	4	3	4	2
Cetyl alcohol	4	4	4	4	4	4	4	4
Lanolin	2	2	2	2	2	2	2	2
Glycerin	2	2	2	2	2	2	2	2
Rose oil	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Nipagin	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18
Nipasol	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Aquadest ad (mL)	100	100	100	100	100	100	100	100

for normal skin (without treatment), positive control (5 % sodium lauryl sulphate (SLS), KC oil, virgin coconut oil, and lotion containing KC oil. As much as 0.5 mL of sample were applied directly to each skin sites. The application sites were then covered with non-occlusive dressing and wrapped with a bandage (semi-occlusive) for 4 h. The observation of the skin reactions for erythema were performed at 24, 48 and 72 h under natural lighting to visualize skin reactions. The skin reactions were described to score the erythema based on the scoring system. The primary irritation score of an animal or primary irritation index (PII) for each sample was determined following the procedure given in the guideline (see supplementary S2).

2.2.6. Skin analysis

Rabbit skin analysis was performed using Skin Analyzer EH-900 U tools. Lotion containing KC oil were applied topically on the skin application site daily for 3 weeks. The skin was analyzed for the percentage of elasticity, moisture, sebum concentration, as well as their sensitivity every week. The software tools provided the percentage and a short description of the skin condition based on the percentage.

2.2.7. Alfa-tocopherol identification and quantification

The identification and quantification of alfa tocopherol was performed using high performance liquid chromatography (HPLC) (Shimadzu) method. The HPLC condition were as follow: Mobile phase: methanol: glacial acetic acid 0.1% (95:5), Stationary phase: ODS C18 column size 250 × 4.6 mm, Maximum wavelength: 295 nm, Column oven temperature: 40 °C, Sample rack temperature: 35 °C; Running time: 20 min with flow rate 1 mL/min. The alfa tocopherol concentration was estimated by measuring average peak area and quantified by linear regression from standard curve of alfa tocopherol.

3. Results and discussion

3.1. KC oil production

The KC oil production by centrifugation method resulted in the KC oil yield comparable to Wong and Hartina (2014) study with characteristics summarized in Table 2. The centrifugation method successfully produced the KC oil.

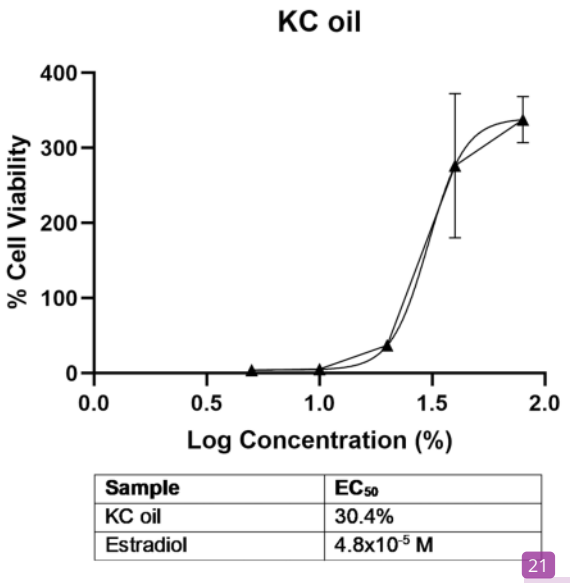
3.2. KC oil exhibited estrogenic activity

The estrogenic activity of KC oil was determined by MCF-7 cell viability assay (MTT method). This method is able to detect and quantify the estrogenic activity of chemicals that bind directly to estrogenic receptors and stimulate the growth of MCF-7 cells (Schilirò et al., 2013; Tatay et al., 2018). MCF-7 cells are ER-positive breast cancer cell lines that allow estrogen in the form of estradiol to bind to estrogen receptors in the cytoplasm and activate the transcription of genes that regulate cell proliferation (Boonchird et al., 2018; Saha Roy and Vadlamudi, 2012; Soto et al., 1995). Thus, estradiol was used as positive control (Jungsukcharoen et al., 2014). The reduction of MTT solution by the succinate dehydrogenase enzyme in mitochondria resulted in color changes which was read as absorbance in the designated wavelength. The color changed from the water-soluble yellow substrate to purple solubilized formazan crystal (Senthilraja and Kathiresan, 2015). The % cell viability of MCF-7 cells treated with estradiol and KC oil exhibited that the higher concentration, the higher the % cell viability. The activity to increase the MCF-7 cell number indicated that KC oil possessed estrogenic activity (EC_{50} = 30.4 %), as it is showed in Fig. 1. The EC_{50} of estradiol was 4.8×10^{-5} M.

The estrogenic activity exhibited by KC oil may be due to the activation of estrogen signaling by the compounds found in KC oil. The prominent component found in KC oil were lauric acid and alfa-tocopherol (Leorna and Israel, 2018; Santoso et al., 1996). Lauric acid was predicted to interact with androgen receptors based on the

Table 2
KC oil yield and characteristics used in the study.

	KC oil
KC meat weight (gram)	1500
Volume KC oil (mL)	96
Yield (%)	6.4
Color	Colorless
Water content (%)	0.26



Sample	EC_{50}
KC oil	30.4%
Estradiol	4.8×10^{-5} M

Fig. 1. Non-linear regression curve of log concentration of KC oil vs. % MCF-7 cell viability. Cell viability was determined by the MTT method with the absorbance measurement at 595 nm wavelength. The GraphPad Prism 9.0 was used to build the graph. Each point represents mean ± SE from triplicate experiments.

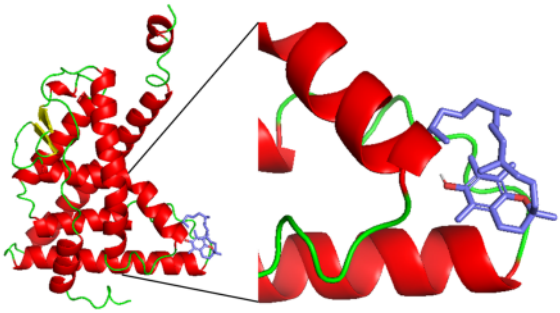


Fig. 2. Visualization of 3D interaction between human estrogen receptor alfa (PDB ID:1A52) (red helix, yellow sheets, and green loop) and alfa-tocopherol (CID_1742129) (blue) with magnification in 20 Å distance. Visualization was built using the PyMol program.

SwissTargetPrediction database (Daina et al., 2019). Androgen receptor is the top 10 protein target for lauric acid (see Supplementary S1.). Lauric acid was reported to prevent benign prostate hyperplasia due to its antiandrogenic activity and stimulate the mamary gland development via estrogenic signaling (Meng et al., 2017; Patil et al., 2016; Sheela et al., 2019).

Alfa-tocopherol possessed interaction with estrogen receptor alfa (Daina et al., 2019), which is also shown in the visualization of its 3D structure in Fig. 2. Other known tocopherols (delta and gamma-tocopherol) inhibit the growth of breast cancer cell line, contrary to the alfa-tocopherol activity, which stimulates its growth (Bak et al., 2017; Khallouki et al., 2016). This was supported by the alfa tocopherol content in KC oil (1.47 g/L) which much higher than what it was found in the coconut oil (0.48 g/L), based on the HPLC method for alfa tocopherol identification and quantification. It was also known that alfa-tocopherol content in coconut oil was very low (Sadu Singh et al., 2020). Thus, high content of alfa tocopherol contributed to the estrogenic effect of KC oil.

Despite the safety concern of estrogenic chemicals contained in cosmetics, the more benefit of estrogenic activity shown by KC oil for topical cosmetic application rules the risk. It is believed that the effects of the topical estrogenic compounds on the skin have more localized action than the systemic effect (Carneiro et al., 2020). In addition, the safety of KC oil is comparable to coconut oil and the derivates, which are considered safe to be used in cosmetics from concentration 0.0001–70 % (Burnett et al., 2011). This is also proved by the primary irritation test result as shown in Table 3. Based on the irritation score, it revealed that the KC oil did not cause any erythema or cause very slight erythema which was not perceptible. Thus, the primary irritation index for KC oil was categorized as negligible, the same index category as coconut oil.

3.3. Optimum lotion containing KC oil formula showed good physical characteristic and benefit to maintain healthy skin parameters

The physical properties of the eight lotion formula designs containing KC oil were analyzed by Design Expert 11.0 to predict the optimum formula. The optimum formula for lotion is shown in Table 4.

Table 3
Irritation score for each rabbit and Primary Irritation Index (PII) from the primary irritation test.

	Irritation Score			PII	Response Category
	1	2	3		
Without treatment	0	0	0	0	Negligible
5% SLS*	1.7	2.3	2.3	2.1	Moderate
Coconut oil	0	0	0	0	Negligible
KC oil	1	0	0.3	0.4	Negligible
Lotion KC oil	0.3	0.3	0	0.2	Negligible

Note: * 5% SLS was used as positive control; h: hours

Table 4
The optimum formula for a lotion containing KC oil.

Lotion composition	%
KC oil	5
Stearic acid (emollient)	6
TEA (emulsifier)	2
Cetyl alcohol (thickener)	4
Lanolin (emulsifier)	2
Glycerin (moisturizer)	2
Rose oil (perfume)	0.5
Nipagin (preservative)	0.18
Nipasol (preservative)	0.02
Aquadest ad 100 mL	

Table 5
Physical characteristics of the optimum formula of lotion containing KC oil.

	Characteristics
Organoleptic	White, semi-solid form, smooth, rosy smell
Homogeneity	Homogenous
pH	6.8 ± 0.04
Spreadability (cm)	6.5 ± 0.15
Stickability (second)	1.21 ± 0.11
Viscosity (cP)	3764 ± 250.59
Emulsion type	o/w
Stability	Stable

Note:o/w: oil in water

Physical properties characterization of the optimum formula was performed, and the characteristics are summarized in Table 5. All of the optimum lotion's physical characteristics containing KC oil formula met the requirements to be developed for topical cosmetic products (Simões et al., 2018). The pH was meeting the required pH for topical application, which ranges from 4.5 to 8.0 (Lukić et al., 2021). Spreadability and stickability are correlated with viscosity. The higher spreadability and the lower stickability will lower viscosity. Lotion spreadability between 5 and 7 cm and stickability was less than 4 s supported the viscosity, which was falling into the requirement of standard viscosity for lotion (2000–50,000 cps) (Iryani et al., 2021).

The lotion stability which was characterized mechanically using accelerated centrifugation for 5 h did not show oil and water phase separation. The stability test experiment was also performed to investigate the lotion stability using cycling test. The test was performed in 6 cycles with dual extreme temperature storage (Romanowski and Schueller, 2001). The KC oil lotion was incubated at 4 °C for 24 h and then moved to the incubator set at 40 °C for 24 h for one cycle. This process was repeated for 6 cycles, and observed the physical appearance of lotion. It revealed that the lotion was stable and no characteristic changes before and after the cycling test.

Skin analysis on the animal study revealed that the lotion containing KC oil were able to maintain parameters for a healthy skin (Firooz et al., 2012). The mean percentage of the animal skin elasticity moisture, and sebum concentration exhibited that KC oil lotion were able to maintain skin normal elasticity, high water content, and balance the oil secretion. The other moisturizer ingredients might also contribute to the characteristic of KC oil lotion to maintain skin elasticity, high water content, and oil secretion.

The estrogenic effect exhibited by KC oil may help the skin to increase its elasticity and smoothen after the lotion product application in the long term. As alfa tocopherol which could bind to estrogen receptor alfa may increase the estrogen receptor activity to stimulate the downstream protein related to collagen production and water resistant (Surazynski et al., 2003). However, further studies to investigate the effector protein by proteomic analysis must be performed. (Table 6).

Table 6
The mean percentage of the elasticity, moisture, and sebum concentration from three rabbits received KC oil lotion topically in week 1, 2, and 3.

Mean Percentage (%)						
	1-week	Description	2-weeks	Description	3-weeks	Description
Elasticity	62.7	Normal elasticity	59.3	Normal elasticity	51.7	Normal elasticity
Moisture	18.3	Higher water content	23	Higher water content	27	Higher water content
Sebum	3	Balance oil secretion	4.3	Balance oil secretion	4.3	Balance oil secretion
Sensitivity*	0	No irritation	0	No irritation	0	No irritation

Note: *sensitivity was defined as score

4. Conclusion

KC oil is possessed estrogenic activity determined by MCF-7 cell viability assay with EC_{50} 30.4%. KC oil in concentration 5% can be applied for lotion preparation with good physical characteristics and pleasant sensory, which is potential for a cosmetic product. In the future, further study in vitro and clinical studies, should be performed to assess the efficacy of KC oil lotion formulation on increasing skin appearance.

CRediT authorship contribution statement

Khafid Mahbub: Investigation, Formal analysis, Writing – original draft, Visualization. **Islamiati Dewi Octaviani**: Investigation, Formal analysis, Writing – original draft. **Ika Yuni Astuti**: Conceptualization, Methodology, Supervision. **Sisunandar Sisunandar**: Conceptualization, Resources. **Binar Asrining Dhiani**: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Writing – original draft, Visualization, Supervision, Funding acquisition.

Declaration of Competing Interest

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

Data Availability

No data was used for the research described in the article.

Acknowledgements

The authors would like to thank Ms. Al Khikmah (COREC UMP) for the help with KC meat preparation, Mr. Rohmadi Budi Setianto for the alfa tocopherol analysis using HPLC, and Ms, Desy Tri Wulandari for the animal handling. This research is partially funded by the Thesis Research Incentive from Faculty of Pharmacy University Muhammadiyah Purwokerto.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.indcrop.2022.115221.

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