BIOLOGY, MEDICINE, & NATURAL PRODUCT CHEMISTRY ISSN 2089-6514 (paper)
Volume 12, Number 1, April 2023 | Pages: 251-258 | DOI: 10.14421/biomedich.2023.121.251-258 ISSN 2540-9328 (online)

Chemical Composition and Evaluation of Anti-tyrosinase and Anti-Oxidative Effects of Topical Cream Formulation from *Acacia sieberiana*, *Vitellaria paradoxa* and Beeswax

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Manuscript received: 30 January, 2023. Revision accepted: 12 March, 2023. Published: 13 March, 2023.

Abstract

Skin diseases can get natural therapies from medicinal plant-based products. In this study, a topical cream was formulated from ethanol extract of *Acacia sieberiana*, beeswax and *Vitellaria paradoxa* (shea) butter. GC-MS characterization with co-injection of the topical cream revealed Stearic acid (31.43%), Palmitic acid (23.15%), Oleic acid (21.44%) and Linoleic acid (16.20%) as the major components. Seven phenolic conpounds were identified and quantified by HPLC- DAD and Ferulic acid (12.81±0.26 mg/g) was the most abundant. The cream showed good antioxidant properties evaluated through β-Carotene-linoleic acid assay, DPPH$^{\bullet}$ radical scavenging, ABTS$^{\bullet+}$ assay, CUPRAC assay, and metal chelating assay. The cream had higher activity in the DPPH$^{\bullet}$ assay (IC_{50} = 32.10±0.84 µg/mL), ABTS$^{\bullet+}$ assay (IC_{50} = 22.49±0.62 µg/mL) and CUPRAC assay (IC_{50} = 49.27±0.79 µg/mL) than α-Tocopherol. The antioxidant effects are an indication that the cream can reduce oxidative stress on the skin including aging, carcinogenesis and inflammation. At 100 µg/mL, the topical cream showed tyrosinase inhibition of 48.23±0.87% regarded as relatively good compared to the standard tyrosinase inhibitor kojic acid, which showed 79.50±0.32% inhibition at the same concentration. The cosmetic cream was able to inhibit the melanin production rate-limiting enzyme, tyrosinase, indicating that it can control hyperpigmentation and skin spots.

Keywords: *Acacia sieberiana*; topical cream; GC-MS; phenolic composition; skin diseases; antioxidant; tyrosinase inhibition.

INTRODUCTION

Skin conditions constitute a real public health problem in the world especially in tropical countries where they represent nearly 30% of consultations (Basset et al., 1999). Skin diseases are considered as health priorities, which can cause significant mortalities, and are generally include fungal infection, stretch marks, eczema, acne, oxidative stress, skin burns, hypopigmentation, hyperpigmentation, melasma and dermatitis caused by cosmetic bleaching agents (Hay et al., 2006). Human skin colour is determined by pigments such as hemoglobin, hemosiderin, carotene and melanins that play protective roles as well as determination of human skin and hair colour (Yamaguchi and Hearing, 2014). Melanin is primarily responsible for skin pigmentation which protects the skin from adverse effects of ultraviolet radiation, skin burn and skin cancer but an over-production or loss of melanin can result in serious skin problems (Zolghadri et al., 2019; Tamfu et al., 2022b). Although melanin has desired effects, an over-production of melanin caused by the action of tyrosinase is undesirable. The production of melanin involves the enzymatic action of tyrosinase and other tyrosinase-related proteins which play a critical role in the process. Tyrosinase, which is a multifunctional copper-containing metalloenzyme is the major rate-limiting enzyme in melanogenesis (Garcia-Jimenez et al., 2017; Alfred Ngenge et al 2021). Tyrosinase causes undesired browning of vegetables and fruits, overproduction of melanin and skin patches and spots (Tamfu et al., 2020b, Masum et al., 2019). Inhibitors of tyrosine are therefore finding applications as attractive cosmetic and medicinal products for skin whitening and depigmentation as well as in agricultural and food industries as antibrowning agents (Zolghadri et al., 2019; Tamfu et al., 2020c). Therefore, tyrosinase inhibition provides solution to perishing of vegetables and fruits as well as therapeutic potential in skin cancers, pigmentation and

neurodegenerative disorders (Masum et al., 2019; Mughal et al., 2022).

Occurrence of reactive oxygen species (ROS) and reactive nitrogen species are at the origin of many human ailments and it is necessary to inhibit their excesses (Tamfu et al., 2021a). Substances which can inhibit the destructive effects of ROS, RNS and free radicals and referred to as antioxidants. Oxidative stress occurs in the situation of an imbalance between ROS and RNS production with respect to antioxidants and the oxidative damage that results from this can spread over most cells and tissues (Talla et al., 2017; Alain et al., 2022; Sawalda et al., 2022). Most antioxidant substances from natural and synthetic sources exist and they are capable of of suppressing ROS and RNS and protect the living systems against oxidative stress (Tamfu et al., 2020d). Synthetic antioxidants like butylated hydroxy toluene (BHT) and butylated hydroxy anisole (BHA) are usually insoluble and associated with side effects, thereby giving way for rising interest in natural antioxidants (Talla et al., 2014; Soni and Loonker, 2022; Tamfu et al., 2021b; López-Pedrouso et al., 2022). Being constantly exposed to external aggressions, the skin represents a privileged target of oxidative stress, which leads to multiple skin damage (Yapi et al 2019; Awadji, 2021). Oxidative stress is one of the main aggravating causes of these conditions, and is one of the potential factors of skin disorders that occur especially with age as well as the early aging of the body defenses. The skin regulates the excretion of waste products, controls body temperature, and protects the organism from environmental, chemical and physical stress factors. The skin is exposed to effects of sun rays, ROS and RNS which can damage the antioxidant defense capacity of the skin causing skin diseases (Kruk and Duchnik, 2014).

Many cases of skin problems are observed in the health care systems worldwide, but some (over 70% of individuals) of the patients with chronic transmissible skin diseases especially in tropical areas do not seek treatment but recourse to medicinal plants and traditional medicine as solution to their skin conditions (Almoshari, 2022). *Acacia siberiana* is one of those plants that pills in northern Benin where it is strongly used in traditional medicine to treat skin conditions. *A. sieberiana*, is a plant of the Fabaceae family, is an essentially thorny ligneous plant. It is native to the savannahs of Africa. This plant can reach 25 m in height whose leaves are 10 to 15 cm long with straight white spines at their base (Orwa et al., 2009). In order to derive a real benefit from the use of this plant, it becomes important to make a formulation for body use based on its extract with judiciously chosen excipients.

The production of home-made medicinal skin ointments from *Vitellaria paradoxa* is popular in most communities in tropical areas of Africa. This work investigates the chemical composition by GC-MS and HPLC-DAD of a topical cream from *Vitellaria paradoxa*, *Acacia siberiana* and beeswax, and evaluation of its antioxidant and anti-tyrosinase activities.

MATERIALS AND METHODS

Plant material and extraction

Acacia sieberiana leaves were collected during the month of January 2021 from North of Benin (Malanville). The plants were identified and voucher specimens prepared by the botanist Professor Hounnankpon Yedomonhan of the Benin National Herbarium where they were deposited under the specimen numbers YH 684/HNB, for *Acacia sieberiana*. The extraction was carried out using ultrasound-assisted extraction with ethanol as solvent. Briefly, 100 g of powdered plant material biomass from each plant were mixed with 1000 mL solvent (H_2O_2/EtOH, 1/1) and sonicated for two hours at 50 °C with Bandelin (Sonorex Digitech device). Further, all the extracts were filtered through Whatman No.1 filter paper and concentrated under vacuum on a rotavapor (Buchi R215) at 50°C. The solid paste extract obtained was stored in the darkness at 4 °C to avoid the degradations until use.

Preparation of topical cream

For the preparation of ointment, the hydroethanol extract of *Acacia sieberiana* was used as the active ingredient. Given the sticky aspect of this extract, 30 g of extract was first dissolved in 100 mL of extraction solvent in order to facilitate the preparation. 25 g of beeswax were melted and added unto the extract. The mixture was blended into a uniform paste at 70°C. 30 g of shea (*Vitellaria paradoxa*) butter were added into the mixture and stirred for further 30 minutes. 5 g of glycerin and 5 g of vaseline were then added while mixing continuously to give a homogeneous pasty ointment. In order to have a perfectly homogeneous mixture, the temperature was maintained at 70°C for 10 min. The ointment was transferred into vials and allowed to cool and solidify before storage. Table 1 shows the components of the topical cream with the percentage composition by mass of each component.

Table 1. Components of the topical cream formulation.

Ingredients	% Composition by mass
Vitellaria paradoxa (shea) butter	30
Vaseline	5
Beeswax	30
Glycerine	5
Ethanol extract of *Acacia sieberiana*	30

GC-MS characterization of the topical cream

The extract (10 mg) was mixed with 150 µL of pyridine and 100 µL of bis(trimethylsilyl) trifluoroacetamide (BSTFA) and heated at 80 °C for 20 min and then the

final supernatant was analyzed by GC-MS (Mercan et al., 2006). An ion trap MS spectrometer and a Rxi-5Sil MS (Restek) fused silica non-polar capillary column (30 m × 0.25 mm I.D., film thickness 0.25 µm) were used for the GC–MS analyses. Carrier gas was Helium with 1.4 mL/min flow rate. The injector and MS transfer line temperatures were 220 and 290ºC, respectively. The ion source temperature was at 200 ºC. The injection volume was 0.2 µL with a split ratio of 20:1. EI–MS measurements were taken at 70 eV ionization energy. Mass range was from m/z 28 to 650 amu. Scan time was 0.5 s with 0.1 s interscan delays. For analysis, the oven temperature was held at 100ºC for 10 min, then increased up to 280ºC with 4ºC/min increments and kept at this temperature for 10 min. Identification of components of the sample was based on GC retention indices and computer matching with the Wiley, NIST-2008 and TRLIB libraries, as well as by comparison of the fragmentation patterns of the mass spectra which reported in the literature and, whenever possible, by co-injection with authentic compounds.

Determination of phenolic profile of the cream

Selected phenolic constituents in the extracts were identified and quantified through reversed-phase high-performance liquid chromatography (RP-HPLC) linked to diode array detector (DAD) as described elsewhere (Küçükaydın et al., 2021; Tamfu et al., 2022c). Summarily, 5 g of each extract were dissolved in water:methanol (80:20), filtered through sterile 0.20 µm filter disk. An Intertsil ODS-3 reverse phase C18 column was used for the separation with a 1.0 mL/min solvent flow rate and 20 µL injection volume. Two mobile phases A (0.5% acetic acid H_2O) and B (0.5% acetic acid in CH_3OH). A gradient elution was applied as follows: 0–10% B (0–0.01 min); 10–20% B (0.01–5 min); 20–30% B (5–15 min); 30–50% B (15–25 min); 50–65% B (25–30 min); 65–75% B (30–40 min); 75–90% B (40–50 min) 90-10% B (50–55 min). A photodiode array detector set at 280 nm wavelength was employed in the detection and the UV data together with retention times were compared with authentic standards. Each analysis was performed three times. A calibration plot established through the elution of known concentrations (range of 0.0~1.0 ppm) of authentic compounds was used in the identification and quantification of the constituent phenolic compounds. Twenty-six phenolic standards (gallic, *p*-hydroxy benzoic, protocatechuic, ellagic, chlorogenic, *trans*-cinnamic, 3-hydroxy benzoic, vanillic, syringic, *p*-coumaric, rosmarinic and ferulic acids; catechin, kaempferol, hesperetin, pyrocatechol vanillin, 6,7-dihydroxy coumarin, coumarin, rutin, myricetin, chrysin, luteolin, apigenin taxifolin and quercetin) were used. The results were expressed as µg per g dry weight of extract.

Antioxidant activity of the cream

β-carotene-linoleic acid method, with a few minor modifications, was used to assess the ability to inhibit lipid peroxidation (Tamfu et al., 2020a) The spectrophotometric evaluation of the $DPPH^{\bullet}$ and $ABTS^{\bullet+}$ radical scavenging activities was conducted as described earlier (Tamfu et al., 2020b) The cupric reducing antioxidant capacity (CUPRAC) was measured using the method as previously described (Apak et al., 2004). BHA (Butylated Hydroxyanisole) and α-tocopherol were employed as reference compounds for comparison of the β-carotene-linoleic acid, $DPPH^{\bullet}$, $ABTS^{\bullet+}$ and CUPRAC assays. The metal chelating activity of the extracts for Fe^{2+} was determined spectrophotometrically (Decker and Welch, 1990). EDTA was used as the reference compound to compare metal chelating activity. Antioxidant activity results were given as 50% inhibition concentration (IC_{50}).

Anti-tyrosinase activity of the cream

The inhibition of tyrosinase enzyme (mushroom source) was determined through the method published elsewhere (**Masuda et al., 2005**) using L-DOPA as the substrate. In a 96-well microplate, 10 µL solution of sample or kojic acid (reference) were added to 150 µL of sodium phosphate buffer (pH 6.8, 100 mM) followed by 20 µL of tyrosinase enzyme and the resulting mixture incubated at 37ºC for 10 minutes. 20 µL of L-DOPA were added after incubation and the absorbances of the resulting solutions were taken at 475 nm and the results expressed as concentration at which 50% inhibition was observed (IC_{50}).

Statistical analyses

Descriptive statistics were applied on the data obtained. Each experiment was done in triplicate and the means of three parallel measurements were deduced. The values given are means±SEM (Standard error of the mean) for three measurements. One-way ANOVA (analysis of variance) was used to compare differences amongst the means and were considered statistically significant $p < 0.05$.

RESULTS AND DISCUSSION

Natural products and medicinal plant extracts are being used as alternative therapies for skin care purposes and are becoming more prevalent in formulations, due to consumers' concerns about synthetic ingredients/chemical substances. The main benefits reported for plant extracts, used in skin care, include antioxidant and tyrosinase inhibition effects amongst others. Due to their uses in skin care products, it is necessary to investigate their chemical composition to guarantee their safety.

GC-MS chemical composition of the topical cream

The volatile constituents of the topical cream were determined by GC-MS and reported on Table 1. A total of thirteen volatile compounds were identified, out of which twelve were fatty acids and one fatty alcohol. Amongst the identified constituents, 61.09% were saturated fatty acids while 37.64% were unsaturated fatty acids together with 1.27% of other compounds. GC-MS characterization with co-injection of the topical cream revealed that, Stearic acid (31.43%), Palmitic acid (23.15%), Oleic acid (21.44%) and Linoleic acid (16.20%) were the major compounds.

Table 3. Chemical profile of topical cream by GC-MS.

No	RI[a]	Compounds	Cosmetic product (%)[b]	Identification methods
1	1152	2-Nonen-1-ol	0.52	Co-GC, MS, RI
2	1160	Benzoic acid	0.75	Co-GC, MS, RI
3	1170	Octanoic acid	1.73	Co-GC, MS, RI
4	1265	Nonanoic acid	0.94	Co-GC, MS, RI
5	1373	Decanoic acid	1.15	Co-GC, MS, RI
6	1492	Suberic acid	0.31	MS, RI
7	1566	Lauric acid	0.77	MS, RI
8	1625	Azelaic acid	0.40	MS, RI
9	1760	Myristic acid	1.21	Co-GC, MS, RI
10	1957	Palmitic acid	23.15	Co-GC, MS, RI
11	2190	Linoleic acid	16.20	Co-GC, MS, RI
12	2195	Oleic acid	21.44	Co-GC, MS, RI
13	2237	Stearic acid	31.43	Co-GC, MS, RI
		Saturated fatty acids	61.09	
		Unsaturated fatty acids	37.64	
		Other compounds	1.27	
		Total	100	

[a]: Kovats index on Rxi-5Sil MS fused silica column, [b]: Percentage concentration, Co-GC: co-injection with authentic compounds; MS: based on comparison with WILEY, ADAMS and NIST 08 MS databases RI: Retention Index literature comparison

HPLC-DAD phenolic composition of the topical cream

The phenolic profile of the topical cream was evaluated by HPLC-DAD with twenty-six standard phenolic compounds, and seven of them were identified and quantified in milligrams per gram of extract (mg/g) and recorded on Table 1. The phenolic compounds Gallic acid (2.70±0.10 mg/g), Chlorogenic acid (3.93±0.07 mg/g), Ferulic acid (12.81±0.26 mg/g), Coumarin (4.10±0.18 mg/g), Rutin (0.39±0.04 mg/g), Ellagic acid (0.17±0.02 mg/g) and Rosmarinic acid (8.48±0.21 mg/g) were identified and quatified. The most abundant consituent was ferulic acid followed by rosmarinic acid and then coumarin and chlorogenic acid.

Antioxidant activity of the topical cream

The antioxidant capacity of the topical cream was evaluated through five complementary assays namely β-Carotene-linoleic acid assay, $DPPH^{\bullet}$ assay, $ABTS^{\bullet+}$ assay, CUPRAC assay and Metal chelating assay and the results presented on Table 3. The cream had higher activity in the $DPPH^{\bullet}$ assay (IC_{50} = 32.10±0.84 µg/mL), $ABTS^{\bullet+}$ assay (IC_{50} = 22.49±0.62 µg/mL) and CUPRAC assay (IC_{50} = 49.27±0.79 µg/mL) than α-Tocopherol which was used as one of the standards, while its activity were relatively close to that of standard BHA as well. The antioxidant activity of the cream was however moderate in the β-Carotene-linoleic and Metal chelating assays. The antioxidant effects is an indication that the cream can reduce oxidative stress and the negative effects of excess reactive oxygen species (ROS) and reactive nitrogen species (RNS) on the skin including aging, carcinogenesis and inflammation.

Anti-tyrosinase activity of the topical cream

Tyrosinase is necessary but excessive tyrosinase is unwanted. Inhibitors of excessive tyrosinase are used in treating skin pigmentation problems and the tyrosinase inhibition of the topical cream was evaluated and the results presented on Table 3. At a test concentration of 100 µg/mL, the topical cream showed tyrosinase inhibition of 48.23±0.87% and this activity can be regarded good when compared to the standard tyrosinase inhibitor kojic acid, which showed 79.50±0.32% inhibition at the same concentration. The cosmetic cream was able to inhibit the melanin production rate-limiting enzyme, tyrosinase, indicating that it can control melanogenesis, skin spots and skin whitening.

Table 2. Phenolic composition of topical cream by HPLC-DAD (mg/g)[a].

No	Phenolic compounds	RT (min)	Cosmetic product
1	Gallic acid	5.70	2.70±0.10
2	Protocatechuic acid	8.75	-
3	Catechin	10.68	-
4	Pyrocatechol	11.04	-
5	Chlorogenic acid	12.35	3.93±0.07
6	p-hydroxy benzoic acid	12.77	-
7	6.7-Dihydroxy coumarin	14.10	-
8	Caffeic acid	15.09	-
9	3- hydroxy benzoic acid	15.98	-
10	Syringic acid	16.56	-
11	Vanillin	17.78	-
12	p-Coumaric acid	20.56	-
13	Taxifolin	21.26	-
14	Ferulic acid	22.14	12.81±0.26
15	Coumarin	24.49	4.10±0.18
16	Rutin	25.30	0.39±0.04
17	Ellagic acid	26.11	0.17±0.02
18	Rosmarinic acid	26.77	8.48±0.21
19	Myricetin	27.35	-
20	Quercetin	30.83	-
21	trans-cinnamic acid	31.33	-
22	Luteolin	31.70	-
23	Hesperetin	32.14	-
24	Kaempferol	33.21	-
25	Apigenin	33.77	-
26	Chrysin	38.40	

[a]Values expressed are means ± S.E.M. of three parallel measurements ($p < 0.05$). [b] -: not detected

Table 4. Antioxidant and anti-tyrosinase activities of topical cream.

Sample	Antioxidant Activity					Anti-tyrosinase activity
	β-Carotene-linoleic acid assay	DPPH• assay	ABTS•+ assay	CUPRAC assay	Metal chelating assay	Tyrosinase inhibition
	IC_{50} (µg/mL)	IC_{50} (µg/mL)	IC_{50} (µg/mL)	$A_{0.50}$ (µg/mL)	IC_{50} (µg/mL)	% Inhibition at 100 µg/mL
Topical cream	18.31±0.53	32.10±0.84	22.49±0.62	49.27±0.79	57.60±0.94	48.23±0.87
α-Tocopherol	2.10±0.07	38.15±0.50	35.50±0.56	60.25±0.55	NT	NT
BHA	1.45±0.03	19.75±0.33	12.80±0.08	25.40±0.40	NT	NT
EDTA	NT	NT	NT	NT	5.52±0.35	NT
Kojic acid	NT	NT	NT	NT	NT	79.50±0.32

Values represent the means ± SEM of three parallel sample measurements ($p < 0.05$).
NT: not tested.

Discussion

Many fatty acids were identified in the topical cream. GC-MS is suitable for the identification of volatile and fatty components of natural extracts and plant samples including fatty acids (Eve et al., 2020; Carol et al., 2017; Koudoro et al., 2022). It could be suggested that most of the fatty acids are coming from the beeswax and shea butter which were used as important matrix components for the production of the cream. Bee products such as beeswax used as component in the production of the skin ointment can suitably be characterized by GC-MS since they are made of volatile constituents (Ngenge et al., 2016). Important skin protective fatty acids such as palmitic acid, linoleic acid, oleic acid and stearic acids were identified as major constituents. Fatty acids and their derivatives are important ingredients in cosmetic

development which act like brighteners, emulsifiers or softeners especially lauric acid, palmitic acid, myristic acid and stearic acid (Yang et al., 2020). Fatty acids act as skin barrier and reduce water loss on skin, prevent entry of harmful substances and can play antimicrobial and anti-inflammatory roles (Cochran et al., 2015). This indicates that the rich fatty acid content of the cream can improve its protective effects on the skin and also avoid entry of bacteria and fungi as well as other objects. It can also control water loss and UV damage.

Phenolic extracts and compounds from plants possess anti-inflammatory and antioxidant effects that reduce the damage caused by oxidative species and prevent skin diseases and aging (Boo, 2019). Phenolic compounds are suitably extracted by using ultrasonic means and identified by HPLC-DAD method and their major interest is due to their antioxidant effects amongst other beneficial activities (Tamfu et al., 2022a). Important bioactive phenolic compounds have been identified in the topical cream and they could be from *A. sieberiana,* a Fabaceae plant which is rich in phenolic compounds and possesses antioxidant effects (Alain et al., 2022; Zongo et al., 2023). The presence of phenolic compounds in the cream could confer oxidative protection and most cosmetologists and dermatologists are searching for safer and more effective natural antioxidants to prevent or treat premature aging and skin diseases. Human skin is exposed to oxidative stress resulting from conditions like sunlight, radiations, pollutants, stress and oxidants which results to aging, wrinkles, excess skin pigmentation and skin tone unevenness (Chen et al., 2021). The antioxidant effect of the cream was evaluated in five different and complementary assays so as to give a global indication of its antioxidant capacity in the different models (Alfred et al., 2020).

The phenolic compounds and fatty acids identified in the cream can act as natural antioxidant, anti-inflammatory, antimicrobial and anti-aging compounds and also as a skin barrier against other biotic and abiotic factors. One important skin problem is irregular spots and pigmentation disorders. Tyrosinase is a copper metallo-enzyme which plays an important role in melanogenesis, over-pigmentation and enzymatic browning and therefore, its inhibitors are used in solving skin disorders, whitening and hyperpigmentation (Panzella and Napolitano, 2021). The topical cream was able to inhibit tyrosinase which shows that it can be used for skin care and skin whitening purposes. Pigmentation determines the color of the skin and UV radiation protection of skin but hyperpigmentation results to spots and melasma, which could be suitably solved by tyrosinase inhibitors. Skin diseases such as dermatitis, acne vulgaris, psoriasis, urticaria, melanoma, keratinocyte carcinoma, scabies and fungal skin diseases can get natural therapies from medicinal plant-based products (Karimkhani et al., 2017; Panzella and Napolitano, 2021; Chen et al., 2021). Skin disorders have significant impacts on the affected person's quality of life especially oxidative damage and skin spots. Skin lightening can be achieved by using natural or synthetic products to improve skin tone, give even skin complexion and reduces melanin production thereby helping patients to treat their skin problems including age spots, acne scars, freckles, skin burns and uneven coloration (Salsberg et al., 2016; Masum et al., 2019).

CONCLUSIONS

The skin is exposed to environmental stress and physical, chemical and biological factors can affect it. Also, in its functions of defense and homeostasis, the skin can encounter negative effects which need to be solved. Many artificial cosmetic and dermatological treatments are available for skin problems but they are expensive and unaffordable to many and also have side effects. For these reasons, many local solutions from medicinal plants and other natural products are available and are used with positive results. In this study, a topical local cream prepared from *A. Sieberiana*, beeswax and other ingredients was evaluated for its chemical compostion by GC-MS, HPLC-DAD as well as its antioxidant and anti-tyrosinase activities. Important fatty acids were identified most of which are relevant in cosmetic science and play a protective role on the skin. Bioactive phenolic compounds were also identified. The good antioxidant and tyrosinase inhibition of the topical crean is attributable to the fatty acids and phenolic compounds whch it contains. The scientifc evidence of the beneficial utility of the skin cream is suggested based on the results and ascertains its use by local populations for various skin disorders as well as wounds and burns.

Acknowledgements: The authors are grateful to Mugla Sitki Kocman University, The university of Ngaoundere as well as University of Abomey-Calavi.

Authors' Contributions: Alain Yaya Koudoro, Theophile Olaye, Pascal Dossa Cokou Agbangnan, Dominique Codjo Koko Sohounhloue and Felicien Avlessi obtained materials, prepared samples, designed the study and carried part of experiments. Alfred Ngenge Tamfu and Selcuk Kucukaydin did the experiments, designed methodologies, analyses, data curation and wrote the first draft. All authors contributed materials, read and approved the final version of the manuscript.

Competing Interests: The authors declare that there are no competing interests.

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