Potential use of Native Fruits Waste from Argentina as Nonconventional Sources of Cosmetic Ingredients

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Abstract:

Background: Collagenase, hyaluronidase, elastase and tyrosinase enzymes are overexpressed and overactive in the skin aging process and hydrolyze the components of the dermal extracellular matrix (ECM) of the skin; these enzymes produce the clinical framework of aging, which includes skin dryness, hyperpigmentation, wrinkles, and inelasticity.

Aims: The aim of this study was to explore the potential use of waste from two Argentine native fruits, namely *Ziziphus mistol*, and red and orange varieties of *Solanum betaceum*, as sources of bioactive compounds.

Methods: Phenolic enriched extracts (PEE) from waste of *Z. mistol* and *S. betaceum* were obtained, and their total contents of phenolics and flavonoids were evaluated. The bioactive properties of the extracts were analysed by measuring their antioxidant capacity and the inhibitory activity on collagenase, hyaluronidase, elastase and tyrosinase enzymes.

Results: The increased ability to inhibit the collagenase was demonstrated by the PEE of *Z. mistol* seeds and peel, while the enzyme elastase was mostly inhibited by extracts of *S. betaceum* skin. *Z. mistol* seed extract was the most active to inhibit hyaluronidase, reaching 96% inhibition at a concentration of 100 μg GAE/mL. The most active extracts to inhibit the tyrosinase enzyme were obtained from the peel of two varieties of chilto fruits, orange and red, and the mistol seed.

Conclusions: The results obtained suggest that *Z. mistol* and *S. betaceum* waste may be considered as a source of bioactive phenolics. Here, Argentine native fruits waste is presented

as a most promising alternative in cosmetic products, with future uses such as hydrogels, creams or lotions.

1. Introduction

Nowadays, fruits and vegetables waste represent both a waste of valuable resources and an environmental problem. Reduction and utilization of food waste in order to obtain value-added products increase the efficiency of the productive process and reduce the associated costs. Through a study, the United Nations Food and Agriculture Organization (FAO) estimated that at least a third of all food produced worldwide (estimated at 1.3 trillion metric tons) is lost and wasted each year; besides, it is worth noting that, among all types of food, the losses and waste of horticultural products are the highest, reaching up to 60% [1]. By-products derived from fruits and vegetables are generally discarded in the form of seeds, pulp, peel or pomace, an occurrence that represents between 10% and 42% of the total raw mass [2]. For these reasons, there is an urgent need to seek value-added resources and uses for these abundant wastes produced globally. The food waste can be acknowledged as a source of natural products and bio-based chemicals such as essential oil and polyphenols compounds that have been extensively studied due to their growing commercial value in nutrition, cosmetic and pharmaceutical industry [3]. Several polyphenols have been associated with different biological activities with a positive impact on health, including antimutagenic, anticarcinogenic, antimicrobial, antioxidant, and anti-inflammatory ones [4,5]. Such compounds include a diversity of phenolic acids, chalcones and flavonoids, namely flavonols, flavones, flavonones, anthocyanidins and condensed tannins [6].

Solanum betaceum Cav. ("chilto", "tomate de árbol", "tamarillo") and *Ziziphus mistol* Griseb. ("mistol", "jabón de palo") are native fruit trees of Argentine Northwest (**Figure 1**). The *S. betaceum* fruits are used in food and medicinal preparations applied topically against tonsil inflammation, for the treatment of anemia, liver and respiratory diseases, and as hypocholesterolemic [7-9]. The mistol fruits are also used as food and in the treatment of hepatic and respiratory affections [10]. The seed and peel are considered waste in juice, pulp or dry pulp powder production. The seed, pulp and peel of both fruits contain phenolic compounds. Two main compounds, rosmarinic acid and caffeoylquinic acid, were identified in peel, pulp and seed of chilto [7,8] (**Figure 2A)**. Flavonoids (kaempferol, spinosin, phloretin and quercetin derivatives) are the major components in peel and seed of mistol [10]

(**Figure 2B)**. Previous studies have shown that phenolics from of peel and seed from chilto and mistol exhibit excellent biological properties such as antioxidant activity, mainly as $HO^{\bullet}$, O^{-}_{2}, H_2O_2, and NO scavengers [7,8,10]. Anti-nociceptive effects of the polysaccharide fractions of chilto fruit pulp were also reported [11]. High yields of chilto seed oil, as well as its unique composition of unsaturated fatty acids and minor components, showed the potential for its application in the food, cosmetic, and pharmaceutical industries [12]. Considering the above, the aim of the present study was to explore, for the first time, the potential of the waste from chilto and mistol fruits as sources of bioactive phenolic compounds as a most promising alternative in cosmetic products in the future.

2. Materials and methods

2.1. Chilto and Mistol Samples

The red and orange varieties of *Solanum betaceum* fruits (common name chilto) were collected from Finca del Obispo, Villa Jardín de Reyes, Jujuy, Argentina, and Horco Molle, Tucumán, Argentina, respectively. Ripe drupes of *Ziziphus mistol* (common name mistol) were collected in Fernández, Santiago del Estero, Argentina. Peel, pulp and seeds from two varieties of chilto and mistol were freeze-dried and powdered. The powders obtained were vacuum-packed and stored at -20 °C until analysis.

2.2. Phenolic compounds extraction

The phenolic compounds from peel, seed and pulp powder of mistol and chilto were obtained by maceration with 95° ethanol (1 g of powder per 5 mL of ethanol) until exhaustion, assisted by ultrasound for 30 min at 25 °C according to Orqueda et al. [7,10]. Then, the mixture was filtered and dried under reduced pressure in order to obtain the phenolic enriched extract (PEE) of each part of the fruits.

2.3. Total phenolic and flavonoids determination

For the quantification of phenolic compounds and flavonoids of mistol and chilto PEE, the methods described by Orqueda et al. [7] were used.

2.4. HPLC-DAD

Although the identity of the compounds present in each PEE was demonstrated in previous works by HPLC MS-MS [7,8,10], a confimation of the major compounds was carried out by using HPLC-DAD. The compounds were monitored at 254 nm and the identification was carried out by comparing the retention times and spectral data (220–600 nm) of each peak with those of standards from Sigma-Aldrich (MO, USA) and Fluka Chemical Corp. (USA). The HPLC system is formed by a Waters 1525 Binary HPLC Pumps system with a 1500 Series Column Heater, a manual injection valve with a 20 μL loop (Rheodyne Inc., Cotati, CA) and a Waters 2998 photodiode array detector (PDA). An XbridgeTM 135 C18 column (4.6 x 150 mm, 5 μm; Waters Corporation, Milford, MA) was used. The solvent system for the separation of components was composed of 0.1% acetic acid in water (A) and 0.1% methanol in acetic acid as follows: 10% to 57% B over 45 min and increasing to 100% B at 60 min. The flow rate was 0.5 mL/min and the volume injected was 20 μL.

2.5. Antioxidant activity

The ORAC (Oxygen Radical Absorbance Capacity) assay was carried out [13] by using AAPH (2,2-Azobis(2-amidinopropane) dihydrochloride) as a peroxyl radical generator. Various dilutions of PEE were mixed with fluorescein (1 μM), and preincubated at 37 °C for 30 min. Then AAPH solution (200 mM) was added. The fluorescence was measured every 2 min during 120 min at 485/520 nm by using a Multi-Mode Microplate Reader (BioTek Instruments, Inc.; Winooski, USA). The antioxidant activity was expressed as μmol Trolox equivalents/g of PEE.

2.6. Antiaging activity

The antiaging activity of PEE obtained from fruits waste was evaluated through the inhibitory capacity of extracts towards related aging enzymes.

2.6.1. Inhibition of the hyaluronidase enzyme (Hyal)

The determination of hyaluronidase inhibition by mistol and chilto PEE was determined by the method described by Orqueda et al. [13]. Sodium phosphate buffer (20 mM, pH 7.0) with sodium chloride (77 mM) and bovine serum albumin (BSA) (0.01%, control) or the PEE were preincubated with hyaluronidase (15 U/mL) for 10 min at 37 °C in a water bath. Subsequently, the assay was started by adding hyaluronic acid (HA) (300 mM). The mixture was incubated for 45 min at 37 °C. Next, 100 μL of HA (undigested) was precipitated with bovine serum albumin (0.1%). The absorbance at 600 nm was measured. Epigallocatechin

gallate (EGCG) (250 μM) was used as the reference inhibitor. The inhibition percentage of the hyaluronidase reaction was calculated.

2.6.2. Inhibition of collagenase enzyme

The inhibition of collagenase enzyme was measured by using the EnzCheck® Gelatinase/Collagenase assay kit (Molecular Probes Inc.) with DQ-gelatin or DQ-collagen type IV substrate. The fluorescence intensity was measured by a Microplate Reader (BioTekInstruments, Inc.; Winooski, USA) each minute during 20 min (485/515 nm). The gelatinase/collagenase inhibition percentage was determined. Oleanolic acid (250 μM) was used as a reference inhibitor.

2.6.3. Inhibition of elastase enzyme

The EnzCheck®Elastase assay kit (Molecular Probes Inc.) was used to determine the effect of PEE on elastase activity. DQ-elastine was used as substrate. The fluorescence intensity was measured. Oleanolic acid (500 μM) was used as a reference inhibitor.

2.6.4. Inhibition of tyrosinase enzyme

In order to evaluate the effect of mistol and chilto PEE on tyrosinase activity, a method described by Orqueda et al. [13] was carried out. Mushroom tyrosinase (333 units/mL) and L-tyrosine solution (2 mM) were used with different PEE dilutions. The absorbance was measured at 480 nm each minute during 20 min. Kojic acid (500 μM) was used as the reference inhibitor.

2.7. Statistical analysis

The experiments were performed by triplicate. Each experimental value is expressed as the mean ± standard deviation. The statistical analysis of experimental data was performed by using InfoStat software (Student Version, 2011). The one-way ANOVA with Tukey post-test at a confidence level of 95% was used to evaluate the rate of differences between samples. The criterion of statistical significance was taken as $p \leq 0.05$.

3. Results and discussion

Today's consumers are increasingly concerned about their health. Therefore, they demand and advocate for the incorporation of bioactive or functional natural ingredients in cosmetics and other formulations to improve their health [14]. The development of natural products

with antioxidant and anti-aging activity is imperative due to the high levels of pollution and UV radiation to which we are currently exposed. An additional issue to take into account, and not one that can be ignored, is the worldwide application of a circular economy for eco-innovation, with a principle of "zero waste", in which waste is used as raw materials for the production of new products. It is for these two reasons that this paper proposes the use of polyphenols obtained from peel and seeds from chilto and mistol fruits for the production of ingredients for cosmetic products.

3.1. Phytochemical characterization of extracts obtained from fruits waste or byproducts

The bioactive compounds present in the byproducts of the agri-food industry, i.e., peel , seeds, pomaces and leaves, can be used for the production of functional foods and cosmetic industry [3]. Seed, pulp and peel PEE from two varieties of chilto (orange and red) and mistol (**Figure 1**) were obtained and characterized. The content of phytochemical compounds was quantified in the extracts of the three parts of the fruits of *S. betaceum* and *Z. mistol* (**Table 1**). The mistol seed, pulp and peel extracts were rich in flavones and flavanols, particularly the seed extracts [10], and richer than the content reported in fruits of *Z. mauritiana* and *Z. lotus* [15].

Besides, the extracts of both varieties of *S. betaceum* were rich in total phenolic compounds, and more abundant in peel of the orange variety and seed of the red variety than the other wastes. The HPLC-DAD profiles of fruits extracts showed the bioactive compounds for both fruits. **Figure 2** shows the chemical structures of the major compounds found in the extracts. The spinosin compound previously detected in the mistol extracts [10] is also found and it is the majority in other *Ziziphus* species, such as *Z. jujuba* [16]. Spinosin, quercetin and kaempferol derivatives, also found in *Z. mistol* extracts, are widely reported for their demonstrated biological activities such as antioxidant, anti-inflammatory and antimicrobial activity [15,17]. Both varieties of chilto presented rosmarinic acid as the main compound in their HPLC-DAD profiles (**Figure 3**). There are numerous reports of interesting biological activities for this compound such as antioxidant, anticancer, antidiabetic, antimicrobial and anti-inflammatory [4]. The feasibility of the extraction of these bioactive components has to be explored to assess the economic viability of supplying these compounds to the cosmetic sector.

3.2. Antioxidant capacity of compounds recovered from waste

All extracts were evaluated according to their antioxidant capacity and the inhibitory potential of pro-aging enzymes. The antioxidant activity of the extracts was assayed by ORAC method, in which a hydrogen atom transfer occurs between antioxidants and free radicals; the results are shown in **Figure 4.** The highest ORAC values were found in the peel samples of both chilto varieties and in the seed extract for the mistol. In the case of chilto orange variety extracts, the greater antioxidant power could be attributed to the amount of phenolic compounds per dry weight of extract present in this part of the fruit [7]. Bravo et al. [18] reported ORAC values for extracts of *S. betaceum* from Colombia (purple and orange) between 353-449 μMolTE/g DW, these being much lower than the two varieties of *S. betaceum* from Argentina (**Figure 4**). Takahashi et al. [19] compared ORAC values of phenolic acid and flavonols separated from fig fruits as 11.13 and 2.15 mmol TE/g, respectively. Differences in the molecular structure of the compounds, including the number or placement of binding hydroxyl groups, may cause differences in antioxidant capacity. This would explain the high ORAC values for chilto orange peel, rich in phenolic acids, mainly rosmarinic acid and caffeoylquinic acid derivatives, compared to mistol seeds, with a high concentration of flavonoids [7,10].

3.3. Inhibitory effect of compounds recovered from fruits waste on proaging enzymes

During the aging process, an imbalance between collagen and elastin production and degradation takes place. Collagen and elastin production decreases while the level of collagenase and elastase that hydrolyzes these components of ECM increases. These molecules constitute the major components synthesized by fibroblast cells, and act to regulate peel strength and elasticity. Matrix metalloproteinases (MMPs) are enzymes of the ECM, which take part in many degradation processes, including those of collagen and elastin. MMP activity is accelerated with age and particularly due to the presence of radicals. Therefore, the search for natural compounds that inhibit the action of these enzymes is crucial. The percentages of inhibition of pro-aging enzymes by seed, pulp and peel extracts of orange and red chilto and mistol are shown in **Table 2**. The increased ability to inhibit the collagenase enzyme was demonstrated by the PEEs of seed and peel of mistol, while the elastase enzyme was mostly inhibited by extracts of orange chilto pulp and red chilto skin (**Table 2**). This result was much weaker than the one reported for *Passiflora edulis* peel and seed extracts, but stronger than the one reported for green coffee extracts [20]. There are reports of the high inhibitory capacity of quercetin on collagenase, a compound that was found in the PEEs of *Z. mistol*; it is even more active than doxicycline, the only FDA-approved collagenase inhibitor

[10]. Shin et al. [21] reported the high ability of quercetin to suppress the expression of UV-induced matrix metalloproteinase-1 (MMP-1). Similar results were reported for kaempferol, present in the extracts of mistol [22]. In the case of the extracts of both varieties of chilto, the inhibitory potency on elastase could be due to the presence of rosmarinic acid, which was able to inhibit elastase by 80% at concentrations of 25 μg/mL [23]. Besides, there are reports that this polyphenolic compound may prevent unfavorable health outcomes, namely, higher risk of development of breast cancer, obesity, gestational diabetes, malignant melanoma, among others, caused by lifelong human exposure to parabens (esters of *p*-hydroxybenzoic acid) contained in cosmetic products [24].

The hyaluronidase enzyme (Hyal) acts on the hyaluronic acid in dermis tissues, weakening them and favoring the expansion of the inflammatory process towards other tissues. The seed extract of *Z. mistol* was the most active to inhibit Hyal, reaching 96% inhibition at a concentration of 100 μg GAE/mL (**Table 2**). This inhibition was greater than that reported for extracts of *Z. mucronata* [25].

Melanogenesis is a peel physiological process that promotes the synthesis of melanin pigments, which plays a crucial protective role against photocarcinogenesis of the peel. In humans, melanin biosynthesis occurs in melanocytes, which contain the tyrosinase enzyme [26]. Pigmentation has a protective role on the peel in UV radiation exposure. However, an increase in pigmentation can develop lentigo, nevus, ephelis among others peel diseases. Like elastase inhibition, the most active extracts to inhibit the tyrosinase enzyme were the peel of both varieties of chilto and the mistol seed (**Table 2**). The tyrosinase inhibition by chilto peel PEE is similar to that reported for extracts of *S. betaceum* from Colombia [18]. Some inhibitors are capable of binding to the tyrosinase enzyme's active site through hydroxyl groups, resulting in changed conformation or in steric hindrance. The antioxidant mechanism of phenolic compounds may also be one of the reasons for tyrosinase inhibition activity [26]. Moon et al. [27] demonstrated that the spinosin, present in mistol seeds PEE act as a competitive inhibitor. In addition, dermatoprotective activity has been reported by inhibiting tyrosinase in fruit extracts of other *Ziziphus* species, with polyphenolic profiles very similar to the Argentine *Z. mistol* [28,29].

3.4. Challenges and potential for developing all these extracts as a cosmetic product

Among new natural products that could be used in skin care such as antioxidant, anti-inflammatory, anti-aging, photoprotective, the edible fruits and its waste, such as peel and seeds, are emerging as cheap and pro-ecological options, since they are rich in bioactive

compounds. Thus, new cosmetic products can be generated through these wastes, giving environmental, social, and economic advantages. In that sense, Latin America has an extraordinary biodiversity of bioactive native edible fruits that could be used as cosmetics and included in international lists of cosmetic ingredients such as those published by the European Commission (CosIng) or Personal Care Products Council (PCPC) but need to be studied to confirm their potential. *S. betaceum* and *Z. mistol* are two widely distributed species in Argentina and South America and from them some products are being industrialized and consequently, waste is being generated. In previous works were demonstrated its antioxidant and anti-inflammatory activities and its potenciality as functional food [7,10]. In these, the antioxidant capacity were confirmed by other methods and the potenciality of phenolic enriched extracts obtained from waste as inhibitor of enzymes involved in the aging process was demonstrated. In addition, the profile of phenolic compounds identified in the fruits and waste indicates the presence of components such as rosmarinic acid, caffeic acid and flavonoids such as spinosin, able to protect the skin against photoaging over a long term [10, 21-23, 27]. Some of them could be used as chemical markers of quality from extracts and the cosmetic products obtained from them. The quantification of these marker compounds would allow authenticating the raw material and eliminating contaminants or adulterants. The compounds could provide ample possibilities of use of this by-product as a source of new ingredients with added healthy properties. The soluble principles yield from seeds and peel of *S. betaceum* and *Z. mistol* was between 25 to 28%, higher than the soluble principles yield in pulps (around 12 to 18%). Likewise, the yield of phenolic compounds in waste (peel and seeds) was higher than the yield of these metabolites in pulp. For this reason, it is important to work at the local level to generate added value for these species and its subproducts and to protect biodiversity. The Sustainable Development Goals (SDGs) propose the transformation of current business models to circular economy and bioeconomy approaches that use responsible sustainability strategies, which aim at the optimal use of biological resources and efficient recycling of residual biomass, taking into account economic, social and cultural aspects [30].

4. Conclusions

The biological potential of native fruits waste of Argentina (chilto and mistol) was proven in this study. The by-products showed a good antioxidant activity and anti-aging activity such as, for example, the inhibition of the activity of collagenase, tyrosinase, elastase and

hyaluronidase enzymes. This study proved to be of great importance for the circular economy model to be fulfilled. The potential applications of waste or subproducts of chilto and mistol in cosmetic industries will surely avoid accumulation and reduce the costs of treatments.

Conflicts of Interest

The authors have no conflicts of interest.

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Legends of figures

Figure 1. A) *Solanum betaceum* red variety, B) *Solanum betaceum* orange variety, C) *Ziziphus mistol* fruits

Figure 2. Structure of some phenolics identified in Argentinean *Solanum betaceum* fruits (A) and *Ziziphus mistol* fruits (B)

Figure 3. HPLC chromatogram of main polyphenols from *Solanum betaceum* orange variety skin (A), pulp (B), and seeds (C) and red variety skin (D), pulp (E) and seeds (F). Detection: UV, 324 nm. Compounds: (1) Caffeoilquinic acid; (2) Rosmarinic acid. The DAD spectrum of compound 1 (G) and compound 2 (H).

Figure 4. Antioxidant capacity of red and orange varieties of *S. betaceum* and *Z. mistol* extracts expressed as μg of Trolox equivalent per gram of dry PEE (μmolTE/g DW). SbO-Seeds: Orange chilto seeds extract; SbO-Pulp: Orange chilto pulp extract; SbO-Skin: Orange chilto skin extract; SbR-Seeds: Red chilto seeds extract; SbR-Pulp: Red chilto pulp extract; SbR-Skin: Red chilto skin extract; Zm-Seeds: Mistol seeds extract; Zm-Pulp: Mistol pulp extract; Zm-Skin: Mistol skin extracts.

Table 1. Content of phytochemical compounds in both varieties of chilto and mistol flours

All data are shown as the mean ± SD of three independent experiments. Different letters (a-g)

Species and varieties	Samples	Yield (g soluble principle/100g)	Phytochemical content/100g of flour	
			Total phenolic compounds (mg GAE)	Flavones and flavonols (mg QE)
***Solanum betaceum* (orange)**	Seeds	17.58±1.02^{b}	179.40±3.02^{a}	175.60±3.10^{c}
	Pulp	12.74±1.56^{a}	415.20±4.05^{de}	223.80±2.90^{e}
	Skin	9.50±0.95^{a}	523.80±3.00^{f}	265.70±3.60^{f}
***Solanum betaceum* (red)**	Seeds	19.69±1.00^{b}	623.60±1.61^{g}	180.50±2.00^{c}
	Pulp	18.70±1.30^{b}	334.00±1.21^{b}	123.3±0.90^{a}
	Skin	8.78±1.50^{a}	408.99±2.30^{d}	195.30±3.65^{d}
Ziziphus mistol	Seeds	8.90±0.81^{a}	425.25±6.00^{e}	444.00±4.22^{g}
	Pulp	18.00±2.05^{b}	356.00±5.15^{c}	130.05±3.33^{a}
	Skin	19.56±2.02^{b}	188.80±4.50^{a}	144.03±3.00^{b}

in the same column show significant differences in the phytochemical content and principle soluble content between each extract according to Tukey's test ($P \leq .05$).

GAE: Gallic Acid Equivalents.

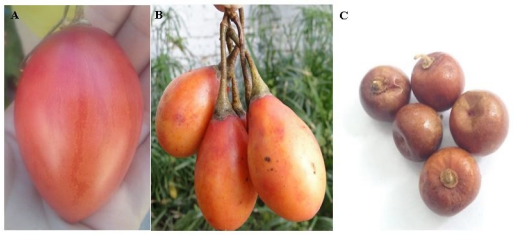
QE: Quercetin equivalents

Table 2. Effect on skin aging-related enzymes of ethanolic extracts of Northwestern Argentinian fruits.

Species and varieties	Samples	Anti-hyaluronidase	Anti-collagenase	Anti-elastase	Anti-tyrosinase
		% inhibition*			
***Solanum betaceum* (orange)**	Seeds	37.36±2.19^{b}	0.00±0.00^{a}	4.39±0.40^{b}	0.21±2.99^{a}
	Pulp	51.94±0.88^{c}	6.90±0.45^{bc}	24.52±1.25^{e}	11.34±2.42^{b}
	Skin	10.69±0.44^{a}	5.61±0.29^{bc}	12.43±0.66^{c}	41.13±3.00^{d}
***Solanum betaceum* (red)**	Seeds	11.00±0.10^{a}	0.00±0.00^{a}	0.00±0.00^{a}	3.98±0.80^{a}
	Pulp	7.28±0.80^{a}	4.92±0.40^{ab}	0.00±0.00^{a}	5.41±0.62^{a}
	Skin	50.70±5.25^{c}	10.17±4.25^{c}	16.12±1.25^{d}	33.10±2.19^{c}
Ziziphus mistol	Seeds	100.00±0.00^{e}	22.47±2.28^{d}	6.51±0.54^{b}	13.14±0.56^{b}
	Pulp	37.05±0.85^{b}	6.71±0.96^{bc}	0.00±0.00^{a}	4.47±1.32^{a}
	Skin	41.39±1.75^{b}	37.71±1.20^{e}	0.00±0.00^{a}	0.82±0.02^{a}
Positive controls	EGCG (250 µM)	69.50±3.00^{d}			
	Oleanolic acid(500 µM)			47.90±4.62^{f}	
	Oleanolic acid(250 µM)		96.84±1.12^{f}		
	Kojic acid (500 µM)				75.60±2.72^{e}

*Percentage inhibition of the extracts at a fixed concentration of 250 μg/mL. All data are shown as the mean ± SD of three independent experiments. Different letters (a-f) in the same column show significant differences in the percentage of inhibition values between each extract according to Tukey's test ($P \leq .05$).

*Control: Oleanolic acid for Collagenase and Elastase, kojic acid for Tyrosinase and EGCG for Hyaluronidase.



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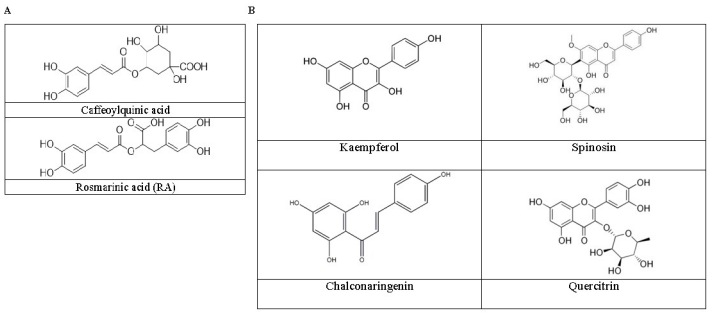

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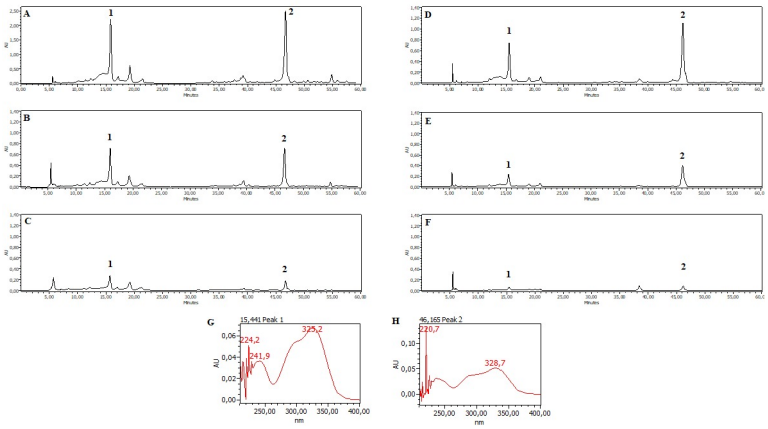

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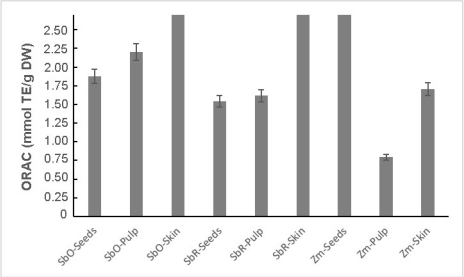

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