J. Cosmet. Sci., 74.6, 315–334 (November/December 2023)

Cosmetic Trends in Dermatology: A Systematic Review of Topical Apple Derivatives in Treating Dermatologic Conditions

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Accepted for publication October 02, 2023.

Synopsis

The apple has been used as traditional medicine throughout human history to treat different medical conditions, including cardiovascular, diabetic, cancer, and inflammatory diseases. Recently, apple extracts and derivatives have been increasingly used in commercial skincare products, touting their properties for enhancing cosmetic effects on the skin. In this review, we systematically searched PubMed, analyzed for inclusion and exclusion criteria, and found 14 articles that described the topical use of apple derivatives on dermatological conditions. It was found that anthocyanin, a compound from apples, as well as apple extract, were found to reduce transepidermal water loss. Procyanidin B-2 and AnnurtriComplex could prevent androgenic alopecia in men and mice, and AnnurtriComplex was effective against chemotherapy-induced alopecia. Phloretin 3',3-disulfonate can attenuate ultraviolet (UV)-induced inflammation, and Annurca polyphenolic extract was found to have a wrinkle smoothing and hydrating effect. However, apple cider vinegar was found to be ineffective in treating atopic dermatitis and caused chemical burns, and apple extract can also induce urticaria and dermatitis. These findings show promise in using apple derivatives for certain skin conditions. However, testing and regulations are needed to prevent adverse effects.

INTRODUCTION

"An apple a day keeps the doctor away" is a centuries-old proverb that is used to encourage health and prosperity by both medical and lay people. It highlights the extensive use of apples, otherwise known as the genus *Malus*, in not only maintaining a healthy lifestyle but also in treating various medical symptoms, including those commonly associated with dermatological disorders.[1] Lately, the use of apple derivatives has increased in the commercial skincare market, prompting a high demand for more information about this product to elucidate whether it has potentially beneficial dermatological effects.

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For many years, apples have been linked to cardiovascular, diabetic, cancer, and inflammatory disease prevention. In particular, apples contain a plethora of antioxidants and bioactive substances that reduce inflammation and cell proliferation in organs such as the liver, lungs, colon, and intestines.[2] Historically, apples, especially in the form of apple cider vinegar, have been used to treat a myriad of ailments including asthma, kidney stones, and even arthritis. The bioactive compounds of apples include fatty acids, polysaccharides, terpenes, carotenoids, polyphenols, and organic acids. These compounds play an important role in establishing the antimicrobial, anti-cancer, antioxidant, and anti-inflammatory potential of apples.[3] In the realm of dermatology, apples and their associated derivatives have been used extensively for stimulating hair growth and for skin regeneration.[4] Polyphenolic extracts are an increasingly popular topic of research for dermatology specialists due to their link to hair growth and keratin production.[3]

Polyphenolic compounds are known to play a regulatory role in many metabolic synthesis processes, particularly those that involve amino acid oxidation. Polyphenols can inhibit certain anabolic processes, such as nucleotide synthesis, to conserve amino acids for keratin synthesis.[3] Paired with a variety of moisturizing and cosmetic products, such as foams and creams, polyphenol extracts can stimulate growth and metabolic activity in hair follicle cells.[4] In terms of apple anatomy, polyphenols are highly concentrated in apple peels. This can be problematic because apple peels are much more susceptible to environmental pollutants when compared to apple pulp. Therefore, the isolation of polyphenols may reduce experimental efficiency and contribute to organic waste and overuse.[4] Nonetheless, the pharmaceutical capacity and benefits that apple polyphenols can provide for patients with different dermatological conditions warrant its further study in medical use and development.[5]

Other apple derivatives, such as their stem cells, have also demonstrated anti-aging and skin regeneration properties. Apple stem cells, used in the form of cosmetic serums, can stimulate anti-wrinkle effects and skin rejuvenation through the metabolic optimization of senescent human fibroblast cells. In other words, the stem cells promote tissue production in aging and otherwise inactive skin cells.[1] The large-scale effectiveness of apple-derived topical serums is still being researched but holds the potential to grow as a lucrative subset of the cosmetic industry, like products containing activated charcoal.

The most marketed form of apple-derived products is apple cider vinegar. Whether for its experimentally supported antimicrobial properties or its association with fad diets on social media, apple cider vinegar is a household name both inside and outside of academia.[1] In dermatology research, apple cider vinegar is speculated to alter skin barrier integrity by acidifying skin and promoting microbial diversification during the healing process.[6] If effective, this treatment could immensely improve the skin barrier of patients with atopic dermatitis and protect them from common bacterial infections, such as those from *Staphylococcus aureus*.[4] With all these potentially beneficial effects, a review of the dermatological treatment of apple derivatives is important both for treatment and in dispelling hearsay.[1] Apple products, though more commonly promoted for their nutritional benefits, are playing a larger role in the cosmetic and medical branches of dermatology. For example, apple bioactive products such as phytosterols are being curated as preventive treatments for squamous cell carcinoma, while also being incorporated into topical products for their moisturization capacity.[2]

Apple products make up a significant percentage of the commercial skincare industry and are among the "trendy" products gaining traction in stores and on social media.[1] According

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to INCIDecoder, there are currently over 1,000 apple-based products that are actively used and marketed to the public.[7] Some common claims about the skincare benefits of apple derivatives tout that it is "rich in AHAs" that rid the skin of "dead skin cells and impurities."[8] Other claims boast that these products can "retexturize, resurface, and reveal luminous skin" and these products have a host of "antioxidants."[9,10] With the projected US $70 billion increase in the skincare market by 2026 (projected by Fortune Business Insights), the need to understand "trendy" ingredients' utility is more important than ever to prevent problematic use by consumers.[11]

To better understand and communicate the efficacy of apple derivatives in dermatological practice, consolidation, and thorough evaluation of existing literature are crucial. In this paper, we are performing a systematic review of publications discussing the varied effects of *Malus* organisms, *in vivo*, on human skin health. We address the limitations and the positive and negative outcomes of each study to better understand the prospects of apple-derived products in not only the consumer market, but also in maintaining the overall health of the integumentary system.

METHODS

72 possible search terms were made by combining terms and using principles of Boolean operators (Table I). Using these terms, a C# .NET console application searched PubMed to query the resulting links through HTTP. All links and publications were collected in July 2022. Duplicates were removed, leaving 209 unique publications. We initially reviewed

Table 1
List of Terms Used to Systematically Search PubMed, Created Using Boolean Operators

skin* topical* "Pyrus malus"	derm* topical* "Pyrus malus"	cosmetic* topical* "Pyrus malus"
skin* topical* Apple	derm* topical* Apple	cosmetic* topical* Apple
skin* topical* "Malus domestica"	derm* topical* "Malus domestica"	cosmetic* topical* "Malus domestica"
skin* topical* "Crab apple"	derm* topical* "Crab apple"	cosmetic* topical* "Crab apple"
skin* apply* "Pyrus malus"	derm* apply* "Pyrus malus"	cosmetic* apply* "Pyrus malus"
skin* apply* Apple	derm* apply* Apple	cosmetic* apply* Apple
skin* apply* "Malus domestica"	derm* apply* "Malus domestica"	cosmetic* apply* "Malus domestica"
skin* apply* "Crab apple"	derm* apply* "Crab apple"	cosmetic* apply* "Crab apple"
skin* application "Pyrus malus"	derm* application "Pyrus malus"	cosmetic* application "Pyrus malus"
skin* application Apple	derm* application Apple	cosmetic* application Apple
skin* application "Malus domestica"	derm* application "Malus domestica"	cosmetic* application "Malus domestica"
skin* application "Crab apple"	derm* application "Crab apple"	cosmetic* application "Crab apple"
hair* topical* "Pyrus malus"	nail* topical* "Pyrus malus"	beaut* topical* "Pyrus malus"
hair* topical* Apple	nail* topical* Apple	beaut* topical* Apple
hair* topical* "Malus domestica"	nail* topical* "Malus domestica"	beaut* topical* "Malus domestica"
hair* topical* "Crab apple"	nail* topical* "Crab apple"	beaut* topical* "Crab apple"
hair* apply* "Pyrus malus"	nail* apply* "Pyrus malus"	beaut* apply* "Pyrus malus"
hair* apply* Apple	nail* apply* Apple	beaut* apply* Apple
hair* apply* "Malus domestica"	nail* apply* "Malus domestica"	beaut* apply* "Malus domestica"
hair* apply* "Crab apple"	nail* apply* "Crab apple"	beaut* apply* "Crab apple"
hair* application "Pyrus malus"	nail* application "Pyrus malus"	beaut* application "Pyrus malus"
hair* application Apple	nail* application Apple	beaut* application Apple
hair* application "Malus domestica"	nail* application "Malus domestica"	beaut* application "Malus domestica"
hair* application "Crab apple"	nail* application "Crab apple"	beaut* application "Crab apple"

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the abstracts using inclusion and exclusion criteria and removed all irrelevant papers. Our inclusion criteria included experiments measuring topical apple derivatives *in vivo* that treated dermatological diseases, that were tested on all species, that included case studies, and were published at any time. Exclusion criteria included experiments that did not have a vehicle or control, trials that focused on *in vitro* and *ex vivo* results, papers that only had histological parameters, reviews, commentaries, any publications that did not present any original data, and articles not written in English. The resultant sum included 21 papers that fit the exclusion and inclusion criteria given.

These publications were read in entirety for their content, which left 14 papers that fulfilled both the inclusion and exclusion criteria (Figure 1). The papers were analyzed for certain data points and limitations, and potential future research was assessed, discussed, and recorded. Data categories that were not included in each study were listed as "not available" (Figure 1).

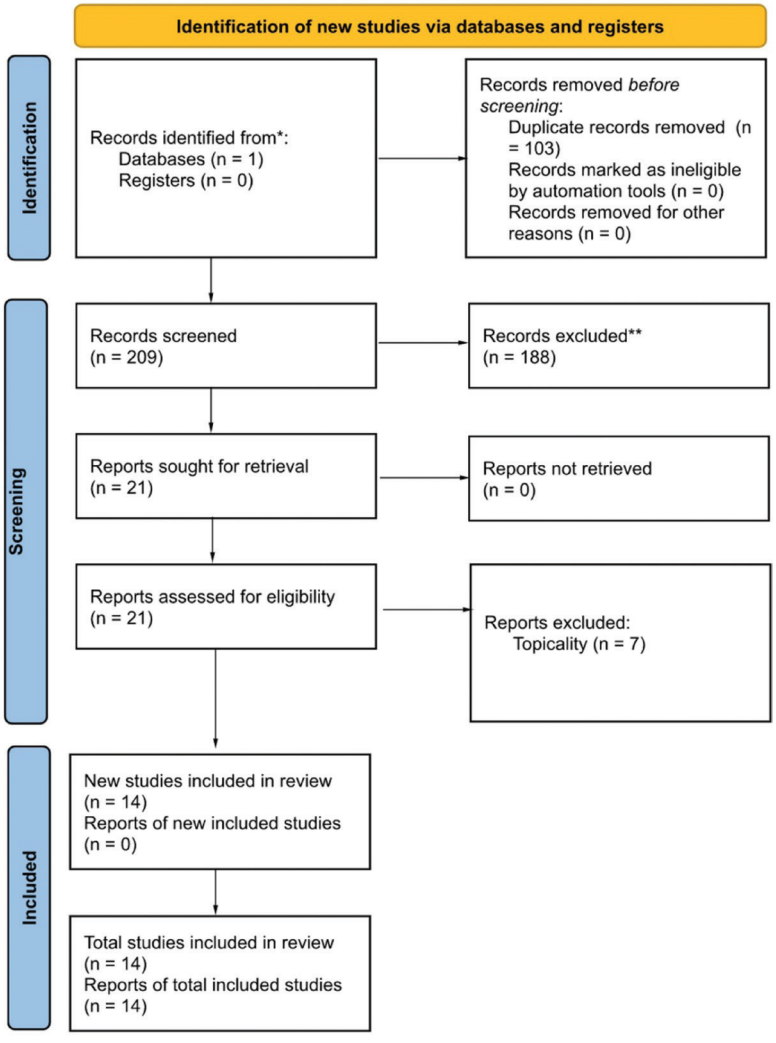

Figure 1. PRISMA Model of the performed methods, updated as of July 2022.

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RESULTS

TYPES OF PUBLICATIONS

A total of 14 publications were included in this systematic review that fit the inclusion and exclusion criteria specified (Table II). The study designs of the publications were as follows: 4 nonhuman experimental trials which included a randomized, placebo-control trial over 28 days, 2 placebo-controlled experimental trials over 28 days, a randomized placebo-controlled experimental study over 28 days, 9 human experimental trials (which included double-blinded placebo-controlled human experimental studies) over 28 days, a double-blind placebo-controlled human clinical trial over 120 days, a double-blind placebo-controlled human clinical trial over 180 days, a positive and negative-controlled human trial over 28 days (with no information on blinding), a placebo-controlled human clinical study over 14 days (with no information on blinding), a placebo-controlled human clinical study over 6 days (with no information on blinding), a double-blind placebo-controlled human clinical trial over 365 days, a single-blinded placebo-controlled human clinical study over 12 weeks, a double-blinded placebo-controlled human clinical study over 28 days, and 2 case reports. The maximum sample size was 43 male subjects of ages 27–58 years old. The length of study ranged between 4 hours to 365 days. 11 of the 15 studies tested the apple derivative in combination with other ingredients, mainly composing a vehicle for the derivative.

APPLE CAN REDUCE TRANSEPIDERMAL WATER LOSS

Three randomized controlled trials assessed the effects of apple fruit extracts in emulsifiers on transepidermal water loss (TEWL) (Table II). One of the studies was a single-blinded, randomized, controlled trial that evaluated the effectiveness of a topical cream containing anthocyanin extract, an apple extract derivative, from the *Malus domestica* fruit (Table II). A total of 12 human subjects of ages 25–35 years, without any skin diseases, were involved in this study. The study included one treatment group and one control group: a 3% anthocyanin extract cream (water-in-oil emulsion with oil phase consisting of 12%–24% paraffin oil, 2–3% Abil EM90, 3% bees wax oil phase, and water phase composed of 3% anthocyanin extract and 100% purified water) treatment group and 0% anthocyanin extract cream (consisting of otherwise same formulation as treatment group) control group.[12] Each group was told to apply their respective creams to their cheeks daily over a 12-week period. Measurements of melanin, erythema, skin moisture content, TEWL, and skin sebum content were taken on weeks 1, 2, 3, 4, 6, 10, and 12. Results revealed that both the treatment group and control group displayed a significant decrease in TEWL ($p < 0.05$), however, there was no significant difference in TEWL between the two groups ($p > 0.05$).[12] The treatment group also displayed a significant mean decrease in skin melanin content ($p < 0.05$) and skin erythema ($p < 0.05$) compared to the placebo group. There was a significant increase in skin moisture content and skin sebum in both the treatment group and control group ($p < 0.05$), however, there was no significant difference in these changes between the two groups ($p > 0.05$).

Another study was a double-blinded, randomized, controlled trial that investigated the effectiveness of wild apple fruit extract on 10 female human participants (mean age of 26.18 ± 5.51 years), with moderately dry skin, and no history of dermatological diseases (Table II).[13] Each participant was told to apply a 6% wild apple fruit extract topical cream

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Table II
Data Points Collected From the Papers Relevant to the Systematic Review

Manuscript	Type of Study	Apple Species	Sample Size	Study Duration	Subject Species	Study Objective	Application	Combined with Anything?	Any Additional Interesting Ingredient Processing or formulation specifics	Controls	Effects on Skin	Possible Mechanisms	Side effects/adverse effects
Badolati et al. – 2018	Experimental study	Malus pumila Miller cv. Annurca	6	4 weeks	Mouse	Patterned hair loss	Topical application of foam applied to the dorsal skin twice a week for four weeks	n/a	The Annurca apple extract used in this experiment is a industrial procyanidinic extract of Annurca apple called AnnurtriComplex which was produced by MB-Med in Turin, Italy	The control used was chemically formulated the same as the experimental foam but it did not contain AnnurtriComplex	Statistically significant increase in mitochondrial activity of hair follicles ($p < 0.001$) and β-oxidation within mitochondria ($p < 0.05$) resulting in increased length of hair follicles	Annurca apple extract reprograms metabolism by inhibiting several NADPH dependent reactions including glutaminolysis, the pentose phosphate pathway, as well as glutathione, citrulline, and nucleotide synthesis in hair follicles leading to alterations in intracellular metabolism and a resultant increase mitochondrial respiration and β-oxidation. Due to this metabolic reprogramming, amino aciad oxidation is reduced and there are larger amounts of them avaiable for keratin biosynthesis.	None
Bunick et al. – 2012	Case report	not specified, apple cider vinegar	1	8 hours	Human	Mollusca contagiosa	Topical application over mollusca contagiosa lesions	n/a	n/a	n/a	Chemical burns	Prolonged exposure to weak acid may cause burns similar to chemical burns seen with strong acids.	Chemical burns
Kamimura et al. – 2000	Double blind clinical study	Malus pumila	29	6 months	Human	Male pattern baldness	Topical application on affected scalp twice a day	n/a	n/a	Placebo (vehicle)	Increase in total and terminal hairs in applied areas	Procyanidin b-2 is a polyphenol known to act as hair-growing factor in murin model both in vitro and in vivo.	None

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Khan et al. – 2021	Single blind clinical study	Malus domestica	12	12 weeks	Human	Transepidermal water loss	Topical application over bilateral cheeks daily	n/a		water-in-oil emulsion: Oily Phase: 16%–24% Parrafin oil, 2–3% Abil EM90, 3% Bees wax; Water phase: 3% Anthocyanin extract, 100% purified water	Placebo (vehicle)	Decrease in transepidermal water loss. Increase in skin moisture content. Increase in skin sebum content. Decrease in skin erythema. Decrease in skin melanin content.	Anthocyanins inhibit tyrosinase activity, suppressing melanogenesis. Beeswax may explain the reduced transepidermal water loss by creating a hydrophobic barrier over the skin. Increase in sebum content may be explained by the paraffin oil used within the formulation, which is a thick viscous oily liquid.	None
Luu et al. – 2019	Controlled clinical trial	not specified, apple cider vinegar	22	2 weeks	Human	Atopic dermatitis	Soaking of one forearm daily for ten minutes in a 0.5% bath	n/a		n/a	tap water	Increased trans-epidermal water loss at 0 and 15 minutes after soaking, which returned back to baseline after 30 minutes. Overall, no improvement in skin barrier integrity was found	Apple cider vinegar is proven to acidify skin which could hold therapeutic potential for patients with atopic dermatitis, who have disrupted skin pH.	Seventy three percent of subjects with atopic dermatitis reported mild skin discomfort of the arm soaked in apple cider vinegar. One atopic dermatitis subject experienced severe pruritus, moderate burning, and erosion on the ACV-treated forearm which resolved within 2 days of discontinuing ACV soaks; the subject did not resume the study. One subject in the control group experienced a nonpruritic papular rash, which resolved without treatment.

(*Continued*)

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Manuscript	Type of Study	Apple Species	Sample Size	Study Duration	Subject Species	Study Objective	Application	Combined with Anything?	Any Additional Interesting Ingredient Processing or formulation specifics	Controls	Effects on Skin	Possible Mechanisms	Side effects/adverse effects
Luu et al. – 2021	Controlled clinical trial	not specified, apple cider vinegar	22	2 weeks	Human	Atopic dermatitis	Soaking of one forearm daily for ten miuntes in a 0.5% bath	n/a	n/a	tap water	Study concludes that daily soaks in 0.5% apple cider vinegar are not an effective method of altering the skin bacterial microbiome in atopic dermatitis	Apple cider vinegar is known to prevent ex-vivo bacterial growth and biofilm formation of various human skin pathogens, including S. aureus.	none
Meynadier et al. – 1982	**Case report**	not specified	1	n/a	Human	Urticaria in atopic patients	Topical application of fruit extract	n/a	n/a	n/a	Contact urticaria	Hypersensitivity seen in atopy can result in the formation of an IgE related reaction involving the skin to foreign allergens like fruits.	Urticaria
Riccio et al. – 2018	Experimental study	Malus pumila Miller cv. Annurca	12	4 weeks	Mouse	Chemotherapy induced alopecia	Topical application of foam applied to the dorsal skin twice a week for four weeks	Combined with water, glycerin, decylglucoside, polysorbate, maltodextrin, potassium sorbate, sodium benzoate, and silica to formulate a foam.	The Annurca apple extract used in this experiment is a industrial procyanidinic extract of Annurca apple called AnnurtriComplex which was produced by MB-Med in Turin, Italy	The control used was chemically formulated the same as the experimental foam but it did not contain AnnurtriComplex	Hair promoting effect.	Annurca apple extract reprograms metabolism in hair follicles shifting the balance towards increased β-oxidation and reduced metabolism through NADPH dependent pathways.As a result, DNA replication and mitosis do not take place increasing the amount of free amino acids for keratin production. Furthermore, Annurca apple extract promotes hair growth by increasing intracellular levels of Prostaglandin F2α through this metabolic reprogramming.	None

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Sanz et al. – 2016	Experimental study	Uttwiler Spatlauber, Malus domestica	32	28 days	Humans	Skin aging	Topical application of serum twice daily for 28 days.	Combined with urea, creatine and palmitoyl tripeptide-38 (Ureadin Fusion Serum Lift Antiarrugas, ISDIN S.A).	n/a	n/a	Dermscan assessment demonstrated a significant mean increase in dermal density of 27% in comparison with baseline evaluation in 78% of subjects on day 28.. Cutometer evaluation showed a significant mean increase in skin elasticity of 10% at 28 days in two-third of the subjects ($p < 0.05$). Corneometer assessment showed a significant increase in skin hydration of 13% and a smoothing effect, with a decrease in roughness of approximately 4% in 71% of subjects after 28 days ($p < 0.01$).	This product increased oxygen consumption and cellular ATP level, indicating an increase in metabolism in fibroblasts. It also significantly decreased the production of mitochodrial reactive oxygen species as well as the extracellular lactate level, which are both reactive species known to damage the skin.	None
Shin et al. – 2014	Experimental study	not specified	18	6 days	Humans/ Human Cell Line	Skin aging	Human: Topical gel applied once to forearm HaCaT Human Keratinocyte: replenished with 1% serum medium including phlorentin 3',3'-disulfonate post UVB-irradiation once.	Silica gel	n/a	Placebo (vehicle)	Reduced UV-induced erythema	Phloretin 3',3-disulfonate may enhance XPA and XPC gene expression, which plays a role in DNA nucleotide excision repair. Phloretin 3',3-disulfonate may play a role in cellular redox reactions by preventing the depletion of glutathione (GSH).	None

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Table II (*Continued*)
Data Points Collected From the Papers Relevant to the Systematic Review

Manuscript	Type of Study	Apple Species	Sample Size	Study Duration	Subject Species	Study Objective	Application	Combined with Anything?	Any Additional Interesting Ingredient Processing or formulation specifics	Controls	Effects on Skin	Possible Mechanisms	Side effects/adverse effects
Stojilijkovic et al. – 2018	Clinical Study	Malus sylvestris fructus	10	28 days	Human	Transepidermal water loss	Topical cream applied twice daily to the forearm.	Two biodegradeable, alkyl-polyglucoside emulsifiers in concentration of 7% and 1.5%.	n/a	Placebo (vehicle)	Increased skin electrical capacitance and no change in trans-epidermal water loss	Polyphenols and fruit acids found in wild apple fruit extract may directly scavenge and neutralize free radicals caused by oxidative stress, inhibit formation of new free radicals, and activate antioxidant enzymes	None
Stojilijkovic et al. – 2022	Experimental study	Malus sylvestris fructus	17	28 days	Human	Transepidermal water loss	Topical cream applied twice daily to the forearm.	n/a	Three cosmetic creams were tested-each had a different concentration of the apple fruit extract. CE6 had 6% concentration of extract, CE12 had a 12% concentration, and CE15 had 15%.	Placebo (vehicle)	Statistically significant increases in electrical capacitance were recorded from application sites of all three formulated dermocosmetic creams containing the wild apple fruit extract at 14 days and 28 days in comparison to the placebo cream and non-treated area ($p < 0.05$).	Polyphenols and fruit acids found in wild apple fruit extract may directly scavenge and neutralize free radicals caused by oxidative stress,inhibit formation of new free radicals, and activate antioxidant enzymes.	None

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Takahashi et al. – 2001	Double-blind clinical study	Malus pumila	29	4 months	Human	Male pattern baldness	1.8 mL of procyanidin B-2 applied twice daily to the subjects' affected area of the head.	n/a	n/a	Placebo (vehicle)	Increased ratio of hairs measuring more that 40 um in diameter ($p < 0.05$); increased mean value of hair diameter ($p < 0.002$); increase in number of total hairs in the designated scalp area ($p < 0.001$); increased hair density over baseline ($p < 0.002$)	Proanthocyanidins, including procyanidin B-2, may stimulate anagen induction to allow for growthpromoting activity.	None
Takahashi et al. – 2005	Double-blind clinical study	Malus pumila	43	12 months	Human	Male pattern baldness	Topical application of 0.7% procyanidin oligmers on affected scalp twice a day	n/a	Procyanidin Oligomers: 7.3% (w/w) procyanidin B-1, 26.2% (w/w) procyanidin B-2, and 7.7% (w/w) procyanidin C-1	Placebo (vehicle)	Greater increase in total number of hairs on affected area in comparison to control. Increase in total number of hairs within treatment group compared to baseline.	Procyanidin might play role in TGF-b pathway which deals with lipid peroxidation and inflammation, both of which are known to aggravate male pattern baldness.	None

(with two biodegradable, alkyl-polyglucoside emulsifiers in concentrations of 7% and 1.5%) over a 9 cm^2 area on their right volar forearm twice daily for 28 days as the treatment arm, and to apply the same topical cream excluding the wild apple fruit extract over a 9 cm^2 area on their left volar forearm twice daily for 28 days as the control arm. Initial measurements of electrical capacitance, TEWL, and pH were taken for baseline values. Repeat measurements were taken after 14 and 28 days following skin application of the treatment and control creams. Results showed there was no significant difference in transepidermal water loss after 14 or 28 days compared to baseline in both the treatment and control arm ($p > 0.05$). The pH of the skin did not significantly change after 28 days in the treatment or control arm ($p > 0.05$) However, the treatment arm showed a significant increase in electrical capacitance ($p < 0.05$), used as an indication of epidermal barrier function, compared to the control arm after 14 and 28 days (Table II).[14]

A third study, a double-blinded, placebo-controlled, nonrandomized, experimental trial, tested the effects of *Malus sylvestris fructus* extract on TEWL, pH, and electrical conductance of the skin (Table II).[13] The study used the extract formulated as part of dermocosmetic creams at 3 different concentrations, 6%, 12%, and 15%. 17 healthy female volunteers (mean age 23.10 ± 3.68), without a history or clinical signs of dermatological diseases, were recruited for the study. After initial measurement of electric conductance, TEWL, and pH of the skin (before the start of the study — basal values), the dermocosmetic creams with extract were then applied to the volar surface of the right forearm in marked areas measured at 9 cm^2, using a cardboard ruler with blank surfaces. The volar parts of the left forearms were treated with placebo. Volunteers were instructed to apply the samples (labeled with stickers, the name, and place of applications) at home twice a day, in the morning and then in the evening (after showering) on the marked surface areas, for 28 days. Measurements were taken after 14 and 28 days of application. Results showed that all three dermocosmetic creams led to a slight reduction in TEWL, but this was not statistically significant. Additionally, pH values of the skin where the dermocosmetic creams were applied remained statistically unchanged as well. However, statistically significant increases in electrical capacitance, measured using a Corneometer® CM 825 (Courage+Khazaka electronic GmbH, Cologne, Germany) and used as an indication of epidermal barrier function, from application sites of all 3 formulated dermocosmetic creams containing the wild apple fruit extract were seen at 14 days and 28 days in comparison to the placebo cream and nontreated area ($p < 0.05$). The dermocosmetic cream with the highest concentration of the extract (15%) demonstrated the greatest increase in hydration. Overall, the study demonstrated that wild apple extract is efficacious in increasing skin hydration when formulated into dermocosmetic creams, as shown by a statistically significant increase in the biophysical parameter of electrical conductance.[13]

APPLE ATTENUATES THE SYMPTOMS OF MALE PATTERN BALDNESS

Three studies investigated the effects of apple derivatives on male pattern baldness. One of the studies was a double-blinded, randomized clinical trial consisting of 29 male subjects (30–57 years old) showing male pattern baldness on the scalp (Table I).[15] Random sampling was used to divide the participants into two groups: treatment and control, at a 2:1 ratio respectively. The treatment group was treated with a 1% procyanidin B-2 agent, extracted from the *Malus pumila* species, while the placebo group received the vehicle used for the

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procyanidin B-2. For 4 months, 1.8 mL of the test agent was applied to the subjects' affected area of the head twice a day. No use of other hair care products except shampoos and rinses was permitted during the clinical trial. Results showed that the increased ratio of hairs measuring more than 40μm in diameter after 4 months of procyanidin B-2 treatment was significantly higher than that of the placebo controls ($p < 0.05$). Nearly 80% of the subjects in the procyanidin B-2 group observed an increased mean value of hair diameter, in comparison to the 30% in the placebo group ($p < 0.02$). The increase in the number of total hairs in the designated scalp area (0.25 cm^2) of procyanidin B-2 subjects after a 4-month trial was significantly greater than that of the placebo controls ($p < 0.001$). 84.2% of the subjects in the procyanidin B-2 group showed an increased hair density, in comparison to 20.0% in the placebo group ($p < 0.002$). The number of total hairs in the designated area (0.5 cm squared = 0.25^2 cm area) after 4 months of procyanidin B-2 treatment significantly increased over the baseline figure for each subject ($p < 0.002$). Comparatively, no significant difference was observed in the placebo controls. Overall, 63.2% of subjects in the procyanidin B-2 group demonstrated hair-growing effects after the 4-month trial, while only 20% of the placebo group demonstrated hair-growing effects ($p < 0.05$).

Another double-blind, randomized clinical study consisted of 29 male subjects experiencing male pattern baldness, and observed the effects of 1% procyanidin B-2 agent, a *Malus pumila* derivative, over 180 days (Table II).[5] The treatment group of 19 men was treated with 2 mL of 1% procyanidin B-2 agent twice a day, while the control group of 10 men was given the vehicle for the 1% procyanidin B-2 only as a placebo. However, this study observed the effects on hair growth for 6 months rather than 4 months. Results showed that the treatment group had a significantly greater increase in the number of total hairs in the designated scalp area in comparison to the control group ($p < 0.005$).[5] The treatment group also had a significantly greater increase in the number of terminal hairs than the control group ($p < 0.02$).[5]

The third study was also a double-blind, randomized clinical trial that tested the effects of procyanidin extracted from *Malus pumila* on 43 men over 12 months (Table II).[16] The study consisted of one treatment group of 22 men who were treated with 0.7% apple procyanidin oligomers twice daily and one control group of 22 men who were given the vehicle used for the procyanidin only as a placebo. The effects of the treatments were assessed at 6 and 12 months. The apple procyanidin oligomers used on the treatment group consisted of 7.3% (w/w) procyanidin B-1, 26.2% (w/w) procyanidin B-2, and 7.7% (w/w) procyanidin C-1. At 6 months, the treatment group showed a significantly greater increase in the total number of hairs in the designated scalp area in comparison to the control group ($p < 0.001$).[16] At 12 months, the total number of hairs in the designated area of the treatment group was significantly increased in comparison to that of the treatment group at the start of the trial ($p < 0.005$).[16]

A fourth study tested the effectiveness of Annurca polyphenolic extract in counteracting patterned hair loss in mice (Table II). The study tested mice with a special foam with AnnurtriComplex® (Mb Med., Turin, Italy), a special procyanidinic extract of Annurca apple.[4] The effects of the foam were analyzed by immunofluoroscopy, scanning electron microscopy, and energy dispersive X-ray. The hair follicles of mice treated with the foam appeared to be increased in length compared to those treated with the placebo. Upon analysis, they showed increased mitochondrial β-oxidation ($p < 0.05$) and increased mitochondrial activity ($p < 0.001$).

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APPLE REDUCES FEATURES OF SKIN AGING, INCLUDING UV DAMAGE AND SKIN WRINKLES

One study investigated the effects of modified apple phloretin derivative, phloretin 3',3-disulfonate, on skin affected by ultraviolet (UV)B damage, using both a HaCaT human keratinocyte cell line and human participants for an experimental study (Table I).[17] For evaluating the effects of phloretin 3',3-disulfonate in the human cell line, HaCaT keratinocytes, which were previously incubated in 1% serum medium for 12 hours, were subjected to UVB irradiation (280–370 nm) and treated with 1% serum medium containing phloretin 3',3-disulfonate. Measurements were taken for up to 12 hours post-UV irradiation. A cell viability assay was performed utilizing 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide conversion to blue formazan to measure viability after treatment with phloretin 3',3-disulfonate. To further evaluate the extent of DNA damage and apoptotic activity in the UVB-irradiated HaCaT Keratinocytes after treatment with phloretin 3',3-disulfonate, the researchers performed a comet assay, cyclobutane pyrimidine dimer quantification test, fluorescence-activated cell sorting analysis, DNA fragmentation assay, western blot analysis, enzymatic caspase activity assay, real time polymerase chain reaction, an inflammatory cytokine assay measuring levels of PGE_2 and IL-6, and checked for intracellular glutathione (GSH) levels.[17] Results showed that treatment with phloretin 3',3-disulfonate significantly reduced UVB-induced cell growth inhibition ($p < 0.01$). Treatment with phloretin 3',3-disulfonate also significantly reduced the amount of DNA damage secondary to UVB irradiation compared to the control group ($p < 0.01$). UVB-mediated apoptosis was largely prevented in HaCaT keratinocytes treated with phloretin 3',3-disulfonate ($p < 0.01$). Lastly, HaCaT keratinocytes treated with phloretin 3',3-disulfonate post-UVB irradiation showed a significant increase in GSH levels ($p < 0.01$) and a significant decrease in COX-2 expression ($p < 0.01$) after 12 hours.[17] The human study consisted of 18 healthy female subjects (mean age 38.7 $\pm$ 7.6 years) with Fitzpatrick skin types I, II, and III.[17] Erythema was induced on both forearms of each female subject with UV radiation followed by a single treatment with 0.05% phloretin 3',3-disulfonate gel (silica gel as the vehicle), and vehicle only as the control, on each forearm respectively. Measurements of the erythema index were performed prior to UV irradiation, on days 0, 1, 2, 3, and 6 after treatment application. Results revealed that the treatment arm showed significantly reduced UV-induced skin erythema 6 days after application of the 0.05% phloretin 3',3-disulfonate gel compared to the control arm ($p < 0.01$).[17]

Another human study among 32 women, with sensitive skin and lateral canthal lines (crow's feet), tested the efficacy of *Annurca* polyphenolic extract in reducing skin wrinkles and increasing skin density, elasticity, and hydration (Table II). An overall increase in skin density was noted by Dermscan (Eurofins Scientific, Luxembourg) in 78% of the women enrolled at the end of the study at 28 days. Cutometer evaluation showed a significant mean increase in skin elasticity from baseline in 67% of the subjects at the end of the study ($p < 0.05$). Corneometer assessment showed a significant increase in skin hydration and a smoothing effect in 71% of subjects at the end of the study ($p < 0.01$).[18]

APPLE CIDER VINEGAR CAN CAUSE CHEMICAL BURNS, WITH UNSURE CAPABILITIES IN TREATING MOLLUSCUM CONTAGIOSUM

A case report described the attempted treatment of molluscum contagiosum lesions with apple cider vinegar (Table II). An 8-year-old male with molluscum contagiosum developed

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chemical burns after his mother placed cotton balls with apple cider vinegar over the lesions for approximately 8 hours.[19] While stronger acids are more likely to cause chemical burns, this case is unique in that a weak acid derived from apples resulted in the chemical burns.[19]

APPLE CAN ATTENUATE CHEMOTHERAPY-INDUCED ALOPECIA

One experimental study tested the effectiveness of an industrial polycyanidic extract of *Annurca* apple (AnnurtriComplex® 6% foam (Mb Med., Turin, Italy) for treating chemotherapy-induced alopecia in mice (Table II). The study found that the apple extract enhances mitochondrial activity in hair follicles, resulting in changes in signaling molecules in the hair follicles. Treated hair follicles damaged by chemotherapy contained structural and molecular similarities to hair follicles undamaged by chemotherapy. It was found that inactivating alterations of prostanoid PGF2α is likely the main contributor in the hair promoting effects of this cosmetic foam.[20]

APPLE CIDER VINEGAR IS NOT EFFECTIVE IN TREATING ATOPIC DERMATITIS

A controlled clinical trial tested the therapeutic potential of apple cider vinegar in improving the skin barrier integrity in atopic dermatitis (Table I). Daily topical 0.5% apple cider vinegar soaks found no long-term effects on skin TEWL or skin pH.[21] The soaks were effective in reducing skin pH, but this effect was not sustained at 60 minutes post-treatment. 73% of subjects with atopic dermatitis reported mild skin discomfort of the forearm soaked in apple cider vinegar. One subject with atopic dermatitis experienced severe pruritus, erosion, and burning of the soaked forearm, which resolved within two days of discontinuing apple cider vinegar soaks. One healthy subject experienced a nonpruritic papular rash which resolved without any treatment.[21]

Another controlled clinical trial tested the potential of apple cider vinegar to alter the skin microbiome in atopic dermatitis on human subjects (Table II). Daily topical 0.5% apple cider vinegar soaks were ineffective in altering the skin microbiome or the abundance of *Staphylococcus aureus* after two weeks.[1]

APPLE EXTRACTS CAN CAUSE URTICARIA AND DERMATITIS

The second case report that was reviewed involved a 16-year-old male with atopy. The topical application of apple, carrot, and potato extracts resulted in contact urticaria periorally on both hands and on the nape.[22] Removal of the extracts cleared any urticaria and dermatitis.[22]

DISCUSSION

According to the current evidence, apple derivatives were found to be effective in treating some dermatological diseases. The strongest evidence was found for treatment of male pattern baldness, which has 4 double-blind clinical trials with more than more than 20 subjects in each treatment group, 3 of which were tested in human males, and one tested in mice. Male pattern baldness, the most common cause of hair loss in men, is a multifactorial

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condition defined by a progressive thinning of hair in a specific pattern that can often be seen as a receding hairline.[23] Procyanidins, like those found in apples, have been found to have growth-promoting effects on murine hair cells.[24] Three of the four reviewed studies looked at how procyanidins could affect the growth of human hair cells and, by relation, could possibly treat male pattern baldness. The results of the studies showed an increased growth in the number of hairs and hair density with no adverse effects when procyanidin was used.[5,15,25] This suggests that procyanidin oligomers have growth-promoting effects on human hair cells and could therefore be used as a safe and effective treatment for male pattern baldness. The fourth study investigated the mechanism of growth-promoting effects of procyanidin B2 on hair follicles in mice. The study used Annurca polyphenolic extract; the Annurca apple species contains one of the highest contents of procyanidin B2.[4] The study found that mice hair follicles treated with Annurca polyphenolic acid underwent metabolic reprogramming, which increased rates of β-oxidation and increased overall mitochondrial activity in comparison to those treated with placebo. This study was able to replicate growth-promoting effects with procyanidin B2 in mice and was further able to prove a mechanism behind those growth-promoting effects. Knowing how procyanidin B2 alters hair follicles, this pathway can be further extrapolated to create more effective treatment options for patients with male pattern hair loss. However, it is uncertain that effects in human hair follicles are the same as those observed in mice hair follicles, therefore further studies in human hair follicles are indicated.[4]

Antioxidant and cosmetic effects of apple derivatives are also supported by evidence that still needs further development in human subjects through long-term study. UV radiation plays a significant role in skin aging, especially photoaging, through skin damage that results from the generation of reactive oxygen species, oxidative damage, and eventual DNA fragmentation in skin cells.[26] Many products have been investigated to determine their efficacy in dampening the features of skin aging. Research has shown that apple derivatives play a promising role in reducing the damaging effects that UV radiation exposure has on the skin. One study by Shin *et al.* revealed that a serum medium containing 1% phloretin 3',3-disulfonate, a modified phloretin derived from apple, significantly decreased UVB-mediated DNA damage, UVB-mediated apoptosis, and UVB-induced cell growth inhibition in HaCaT keratinocytes. The mechanism that explains this finding is suspected to involve the upregulation of *XPA* and *XPC* genes, which play a major role in nucleotide excision repair after DNA damage.[17] Moreover, the study revealed that treatment with phloretin 3',3-disulfonate post-UVB irradiation resulted in an increase in GSH levels and a significant decrease in COX-2 expression. GSH is an endogenous tripeptide that plays a major role in scavenging free radicals to protect cells from oxidative damage. The increase in GSH in the UV-irradiated HaCaT keratinocytes suggests that phloretin 3',3-disulfonate may participate in the modulation of cellular redox signaling and cell death activation by preserving the GSH levels within the cells.[17] Furthermore, COX-2 is an important enzyme that produces pro-inflammatory mediators in response to attacks on the body. The reduction in COX-2 expression in UV-irradiated HaCaT keratinocytes indicates that phloretin 3',3-disulfonate may have an effect on the inflammatory pathway, reducing the potential for further damage from prolonged intracellular exposure to inflammatory mediators.[17]

A human clinical study also performed by Shin *et al.* demonstrated that treatment with 0.05% phloretin 3',3-disulfonate gel significantly reduced UV-induced skin erythema after 6 days. Phloretin 3'3-disulfonate is known to have antioxidant and anti-inflammatory properties (as

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shown by Yang *et al.* and Chang *et al.*), and this was further demonstrated through studies with HaCaT keratinocytes.[17] This study allowed for the macroscopic evaluation of the effects of phloretin 3'3-disulfonate. Another human clinical study demonstrated the effects of Annurca polyphenolic extract, an industrial procyanidinic extract, on wrinkles and reduced skin density, elasticity, and hydration in women. The study found an overall increase in dermal density, skin elasticity, and skin hydration among subjects along with reduction of crow's feet and skin roughness.[18] The study found that the apple extracts optimized metabolism in senescent fibroblasts by increasing cellular oxygen consumption and ATP level while also reducing extracellular lactate levels, restoring full cell function, which resulted in the anti-aging properties of the serum. However, the serum also contained pro-collagen lipopeptide, creatine, and urea which are also known for having cosmetic anti-aging effects.[27-29] Any of these ingredients could be responsible for the metabolic optimization, hydration, or cosmetic effects observed in this study.[18] Further studies are indicated for testing the lone effects of Annurca polyphenolic extract for the reversal of skin wrinkles and increased dermal density.

The evidence that apple derivatives work for chemotherapy-induced alopecia is poor, since most of the current information is tested only in mice. Chemotherapy-induced alopecia is a common side-effect of chemotherapy which can be distressing for the patient, can lead to social and sexual dysfunction, as well as anxiety and depression. Furthermore, typical treatments for alopecia usually involve hormones and growth factors which could provide unwanted protection of tumor cells or worse, could induce cancer cell proliferation, and thus are not an option for patients undergoing chemotherapy. Annurca polyphenolic extract was found to have a hair promoting effect that resulted in metabolic reprogramming of hair follicles.[20] This reprogramming increases β-oxidation and reduces metabolism through NADPH dependent pathways, allowing more amino acids to be present for keratin formation and more prostaglandin F2α intracellularly, which also promotes hair growth. Due to its mechanism of action, DNA replication and mitosis are not affected by *Annurca* polyphenolic extract, making it a potential treatment option for those experiencing chemotherapy-induced alopecia. However, it is uncertain if the mechanism of action of *Annurca* polyphenolic extract is the same in human hair follicles as in mice hair follicles. Therefore, further studies are indicated in humans and in the efficacy of this extract against chemotherapeutic regimens, other than Paclitaxel and Docetaxel.

Apple derivatives were found to be ineffective in molluscum contagiosum, TEWL, and atopic dermatitis, and often lead to more irritation or skin damage. The presence of a damaged skin barrier seems to predispose further inflammation due to the skin's inability to protect itself against the potentially corrosive effects of acidic apple derivatives, such as apple cider vinegar.

Molluscum contagiosum is a self-limiting skin condition resulting from a molluscum contagiosum virus infection that is marked by pink umbilicated papules.[30] In the reviewed case report, the topical application of apple cider vinegar to treat Mollusca contagiosum resulted in chemical burns similar to that of a stronger acid, despite vinegar being a weak acid.[19] The severity of the tissue damage by a weak acid may be attributed to the extended contact the acid had to the skin ($t = 8$ hours), the preexisting molluscum contagiosum lesions that could have weakened the skin barrier, or some component in apple cider vinegar that adds to the causticity of the acid. However, to determine the true effects of the apple-derived acid on the lesions, there needs to be further studies investigating the effect of the length of topical contact, molluscum contagiosum lesions, and components of apple cider vinegar on the skin barrier. As this is a case report based on a single subject, the studies

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would need to also involve more subjects to reduce the chances of error and other variables from affecting the results.

TEWL is commonly evaluated in various dermatologic diseases that present with skin barrier dysfunction, but there is little current evidence that supports apple derivatives' efficacy in reducing TEWL.[13,31,32] A study evaluating the effectiveness of apple-derived 3% anthocyanin extract cream on 12 subjects revealed a significant decrease in TEWL after application for 12 weeks, but there was no significant difference between the treatment and placebo group.[12] The protection from TEWL in both treatment and placebo groups in this study could be explained by the beeswax present in the topical vehicle. Beeswax is found to have hydrating properties due to its richness in vitamin A and its ability to form a hydrophobic barrier over the skin.[33]

Atopic dermatitis is a chronic skin condition and involves a strong genetic predisposition, multiple immune pathways, T-cell inflammation, and epidermal dysfunction.[34] Two studies tested the efficacy of apple cider vinegar as a treatment option for atopic dermatitis. One study found an unsustained reduction in skin pH immediately after treatment with apple cider vinegar, mild discomfort of the treated area treated, and one subject had a severe reaction to apple cider vinegar resulting in their discontinuation from the study.[21] The second study found that apple cider vinegar had no altering effects on skin microbiome in atopic dermatitis patients and no adverse effects to the daily 10-minute soaks.[1] The limited sustainability of skin pH reduction and ineffectiveness in altering skin microbiome could be due to the dilution of apple cider vinegar to perform soaks (as instructed in the study), or the short time of contact with dilute apple cider vinegar. Furthermore, a significant number of subjects with atopic dermatitis in one study showed mild adverse effects to the treatment with only 10 minutes of contact, and one subject experienced severe pruritus. The irritating effects of apple derivatives were further supported by a case report, where topical applications of apple extract resulted in contact urticaria in a 16-year-old male with atopy, which cleared with removal of contact with the extract.[11] This case could indicate that patients with atopy might have increased risk of reaction or increased sensitivity to apple extract and could potentially explain the subject's skin discomfort resulting from contact with apple cider vinegar. If proven, this could eliminate apple cider vinegar as a potential therapeutic for patients with atopic dermatitis. To determine the true effect of apple cider vinegar, further studies should investigate the concentration and duration of contact with the weak acid with a larger treatment population.

There are a few limitations within these studies that require further study before apple derivatives can be established as a therapy or used in commercial or drug products. Each study involved less than 100 subjects, and with such a small sample size, confounding variables can misrepresent the true effectiveness of the apple derivatives. Adverse effects can also be overlooked if there is not a wider range of subject ages, gender, and skin types involved when testing for safety. Also, the effectiveness of different dosages is still yet to be investigated. In addition, some apple derivatives, such as apple cider vinegar, are found to be corrosive for the skin and should be warned against use by the public.

CONCLUSION

Even with these limitations, apple derivatives, most notably 1% phloretin 3',3-disulfonate and procyanidin oligomers, show promise in increasing hair growth and decreasing

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photooxidative damage, and warrant further study. With the extensive marketing touting the benefits of apple derivatives to consumers, this systematic review extensively searched and condensed the effects of apple derivatives to inform medical professionals and the public of the current evidence for its use in cosmetic or pharmaceutical science. Further research into the compounds in these derivatives can elucidate mechanisms of use found in apples, a cheap and commonly used fruit that has been used for skincare for centuries.

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