

Review Article

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Allergic contact dermatitis from selected topical medicaments: A brief review

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ABSTRACT

Adverse cutaneous reactions, some of which are allergic in origin and of variable severity, occur from systemic administration of medicaments, and others result from contact sensitivity from their topical use. Allergic contact dermatitis (ACD) to topically applied medicaments, excipients or active ingredients, is encountered frequently in clinical practice and should be suspected in all at-risk individuals. Although about one-third of all cases of ACD are initiated or perpetuated by prescribed or non-prescribed topical preparations, the problem usually remains underappreciated. The prevalence of hypersensitivity to these allergens varies across regions and periods of time depending on the personal habits and health-seeking behavior of an individual, the interest of the clinician in the field of contact dermatitis, and the types of cases studied. Often promoted by social media influencers as a remedy for all dermatological problems or cosmetics, the use of several home remedies and other over-the-counter antiaging and cosmetic products has increased exponentially in recent years. We, herein, briefly review some of the commonly used products potentially causing ACD.

Keywords: Allergic contact dermatitis, Aluminum, *Aloe vera*, Alpha lipoic acid, Allantoin, *Azadirachta indica*, Calcineurin inhibitors, Caladryl, Capsaicin, Curcumin, Eflornithine, 5-fluorouracil, Heparin, Idebenone, Lanolin, Minoxidil, Natural oils, Nitroglycerine, Petrolatum, Propolis, Retinol, Selenium sulfide, Sulfur, Urea, Vitamins, Zinc pyrithione

INTRODUCTION

The use of several home remedies and other over-the-counter (OTC) anti-aging/cosmetic products has increased exponentially after social media influencers have been promoting them as remedies-for-all dermatological disorders or as cosmetics in recent years. However, adverse cutaneous reactions, including contact dermatitis from them, especially in at-risk individuals [Table 1], remain underappreciated even among clinicians. We, herein, briefly review some of the commonly used products potentially causing allergic contact dermatitis (ACD).

REVIEW OF THE LITERATURE

An online search using Google, PubMed, MEDLINE, and IndMed was carried out for medical literature published in the English language in the past 20 years describing case reports, case series, and other studies. The search terms included "topical medicaments (see keywords)," "adverse cutaneous reactions from topical medicaments," and "contact allergy to topical medications" using comma separated value function. In addition, relevant standard textbook chapters and cross-references of the published articles were also reviewed.

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ALUMINUM

Although it has been named the allergen of the year 2022, sensitivity to aluminum remains unappreciated.^[1] The chloride and nitrate salts of aluminum have more irritant potential than the chlorhydrate, allantoin, and citrate. Sensitization to aluminum salts usually occurs from cosmetics (antiperspirant sticks), pentavalent vaccines (diphtheria (D), pertussis (P) and tetanus (T) (DPT), poliomyelitis, and hemophilus influenza B), aluminum precipitated allergens for hay fever desensitization, used preparations and medicinal as antibacterials, antiperspirants, astringents, and antacids. Contact allergy to aluminum can occur in 1% of vaccinated children and presents as pruritic subcutaneous nodules months after the vaccination and often shows exacerbations during infections.^[2] Hyperpigmentation, hypertrichosis, and localized or widespread dermatitis are other manifestations.^[1,3,4] Aluminum sensitivity also has significant implications for patch testing practices. Patch testing is usually recommended with aluminum chloride hexahydrate 2% (pet.) for children and 10% (pet.) for adults.^[5] Reactions to the aluminum-disc chambers may occur in sensitized individuals and should be suspected when all patches in the Finn chamber patch test system develop a positive reaction or angry back phenomenon.^[6,7] False positive or irritant reactions may occur when testing mercury in aluminum discs due to mercury-aluminum complex formation.^[8]

ALPHA LIPOIC ACID (ALA)

ALA has become popular across countries for its reported antioxidative and protective effect on photo-aged skin and other tissues. It has been used in many OTC anti-wrinkle creams but remains a rare contact sensitizer. Bergqvist-Karlsson *et al.*^[9] have reported a case of severe dermatitis involving the eyelids, trunk, and arms following the use of ALA, or 1,2-dithiolane-3 pentanoic acid.

ALOE VERA EXTRACT

A. vera (*Aloe barbadensis*, Family Liliaceae), a native plant of the North African and Arabian Peninsula, is an herbal product used worldwide for its supposedly antiinflammatory and anti-microbial properties for healing wounds, psoriasis, radio dermatitis, and in moisturizing creams, and several cosmetic products.^[10] Its bark and leaves contain antrachinones that have a considerable potential to cause irritant and allergic dermatitis. The leaf pulp in the center has the least irritant potential and high carbohydrates and water contents and is incorporated in various personal care products. There are few reports of ACD from topical application of *A. vera*, especially *Aloe arborescens*.^[11,12] A widespread leg dermatitis has occurred following *A. vera* application for stasis dermatitis.^[13] Ferreira *et al.*^[14] describe a patient with venous insufficiency who developed leg dermatitis and eyelid erythema following the application of raw *A. vera* juice over the legs. Patch testing with aloe leaf and macerated aloe jelly produced a positive reaction.

ALLANTOIN

Allantoin finds use as an active ingredient in many OTC cosmetics and topical medications advocated for psoriasis for its moisturizing and keratolytic effects. It is a uric acid derivative (diureide of glyoxylic acid). It increases the water content of the extracellular matrix, promotes cell proliferation and wound healing, and has a soothing, anti-irritant, and skin-protecting effect by forming complexes with irritant and sensitizing agents. Allantoin-containing topical non-steroidal preparation is effectively used for providing relief from pruritus in mild-to-moderate atopic dermatitis.^[15] It is non-irritating, non-toxic, and non-allergenic.^[8]

CALAMINE

CaladrylTM lotion containing calamine and diphenhydramine is a bland, antipruritic lotion used in dermatology for urticaria, insect bite reactions, etc., for its soothing effect. Contact dermatitis from calamine per se is not reported, but diphenhydramine, an H₁ antihistamine, is known to cause contact sensitivity and photosensitivity. Gupta *et al.*^[16] reported ACD with exfoliation in a 9-year-old girl secondary to Caladryl. However, they did not confirm whether contact sensitivity was exactly due to calamine or diphenhydramine.

CAPSAICIN

It is an alkaloid (capsaicinoid) derived from the seeds and membranes of chili peppers (genus Capsicum, family Solanaceae) and used topically (0.025-0.15%), alone or in combination with doxepin (3.30%), or camphor and menthol (0.025%) as an analgesic for neuralgic pain (post-herpetic neuralgia, diabetic neuropathy). It causes the release of substance P from C fiber afferent neurons. Repeated applications reversibly deplete stores of substance P and reduce pain transmission from peripheral nerve fibers to higher centers. It is also effective in reducing itching and inflammation in psoriasis.^[17,18] Depending on the concentration used, its clinical effects vary between a feeling of warmth and a burning sensation. Application site irritation, edema, tingling, burning and stinging, and cracking and scaling are common adverse effects. Contact dermatitis (Hunan syndrome) has occurred from the direct handling of chili peppers containing capsaicin.^[19]

CURCUMIN

Curcumin and bisdemethoxycurcumin are two lipophilic polyphenol curcuminoids of turmeric (*Curcuma longa*).

Turmeric has been used in spices for cooking, and topically and orally in India as a home medication for its antioxidant, anti-inflammatory, anticarcinogenic, antidiabetic, antibacterial, antifungal, antiprotozoal, antiviral, antiulcer, and anticoagulant properties.^[20] Allergic and pigmented contact dermatitis from turmeric in food, cosmetics, and occupational settings has been reported.^[21,22] ACD with and without photo-aggravation from kumkum, which contains turmeric as a major ingredient or turmeric *per se* in the ritual thread, has been reported in Indian women.^[23,24]

EFLORNITHINE

Eflornithine HCl (13.9%) cream is used for the reduction of unwanted facial hair in women, but it is not depilatory. It irreversibly inhibits skin ornithine decarboxylase enzyme activity necessary for the synthesis of polyamines and cell division and retards the rate of hair growth. It does not have contact sensitizing, photocontact allergic, or phototoxic properties but can cause application site stinging, pruritus, erythema, edema, irritation, dryness, acne, folliculitis, pseudofolliculitis, and cheilitis in a few patients.^[25]

5-FLUOROURACIL (5-FU)

The 5-FU 1%, 5% usually elicits irritant contact dermatitis at the site of application characterized by erythema, burning, stinging, pruritus, and scaling. The ACD to 5-FU or one of the ingredients of topical preparation has been reported infrequently. Meijer and de Waard-van der Spek^[26] reported eight of 14 patients having ACD with positive patch tests from the active ingredient and another four patients reacting to vehicle components.

HEPARIN AND HIRUDIN

These are used for their anticoagulant activity. Hirudin is derived from leeches and finds use as an anti-inflammatory agent in ointments for treating hemorrhoids or thrombophlebitis. Allergic reactions from both fractionated and unfractionated heparin are not rare and usually manifest as eczema at the injection site or after topical application of heparin-containing gels.^[27] Cross-reactions between fractionated and unfractionated heparin are known, but patients sensitive to heparin are known to tolerate hirudin better.^[28] ACD to hirudin has been reported, and a positive patch test reaction was observed with 20% raw hirudin in ethanol.^[29]

IDEBENONE

Idebenone (hydroxydecyl ubiquinone) is a low molecular weight synthetic analog of coenzyme Q10, which is a potent antioxidant. It inhibits lipid peroxidation, maintains mitochondrial electron transport, and stimulates nerve growth factor. It prevents free radicals from damaging the collagen and elastin in the skin and additionally inhibits melanin production by the melanocytes.[30,31] Idebenone (0.5-1%) cream is used for the treatment and prevention of photoaging, fine lines, and wrinkles. It is well tolerated by the established protocol of cosmetic safety testing including repeated insult patch testing. Skin irritation, erythema, itching, burning, and swelling may occur in individuals with pre-existing dermatitis or who have sensitivity to cosmetics or jewelry. Patch test positive ACD from anti-wrinkle cream containing idebenone has been reported.^[32] Positive patch test reactions both from idebenone 0.5-1% (pet.) and the implicated cosmetics were reported more often in patients with face/neck dermatitis due to idebenone containing antiaging cream.[33-35]

LANOLIN

Lanolin (syn. wool fat, wool grease, wool wax, wool alcohol, and adeps lanae anhydrous) is a naturally occurring product derived from sheep wool/fleece. It is a complex mixture of esters and polyesters of 33 high-molecular-weight alcohols and 36 fatty acids.^[8] Its main constituents include sterols (lanosterol, cholesterol, and agnesterol), fatty alcohols, and fatty acids. It finds use in several medicaments for topical application and is considered a weak sensitizer. Occupational contact dermatitis has not been observed in wool sorters or workers involved in collecting, refining, or transporting wool wax.^[36] Allergic contact sensitivity from lanolin is perhaps more frequent when used in medications for atopic dermatitis, stasis dermatitis, and ulcers than in patients with non-eczematous dermatoses such as psoriasis and lichen planus.^[8] Acetylated lanolin (modulan), dewaxed lanolin (lantrol), and hydrogenated lanolin are its modified forms and are considered less sensitizing.

MINOXIDIL

Minoxidil is a potent vasodilator resembling hydralazine. Topical minoxidil (2%, 5%, and 10%) in propylene glycol, ethanol, and water has been used for the treatment of androgenetic alopecia in men and women. Headache, dizziness, hypotension, and breathlessness occur following topical application in a few individuals. Hypertrichosis and allergic and photo-ACD have been associated with its topical use and occupational exposure.^[37,38] Propylene glycol enhances percutaneous absorption of minoxidil, and the combination perhaps accounts for increased chances of contact sensitivity. Patch testing with minoxidil in petrolatum generally produces negative results but the addition of propylene glycol has elicited more positive results.^[39] Sánchez-Motilla *et al.*^[40] have reported pustular allergic dermatitis from minoxidil.

NATURAL OILS

Castor oil, Jojoba oil, Juniper oil (oil of Cade), Peppermint oil, Olive oil, Sesame oil, Tea tree oil, and Neem oil are used in several topical medications and cosmetics as skin lubricants, emollients, hair conditioners, wrinkle remover, and herbal treatment for skin disorders. Castor oil in cosmetics, mainly lipsticks, can cause ACD, or allergic cheilitis from ricinoleic acid.^[41,42] Eucalyptus oil, an essential oil obtained by steam-distillation of the leaves and terminal branches of Eucalyptus species, mainly Eucalyptus globulus Labill (family Myrtaceae, subsp. globulus), is widely used in topical antiseptics, liniments, soaps, mouthwashes, lozenges, balms and inhalants for flu, hand cleaners and wipes, aromatherapy, and cleaning products. Eucalyptol (1,8-cineole), a monocyclic monoterpene ether, is the principal constituent comprising 70-90% of the volume of pharmaceutical-grade eucalyptus oil. Limonene, cuminyl aldehyde, α-pinene, α-phellandrene, *p*-cymene, *trans*-pinocarveol, and terpinen-4-ol are other constituents.^[43] Terpinen-4-ol is also the main constituent in tea tree oil. ACD from eucalyptus oil is perhaps underreported and showed a prevalence of 0.25% over 9 years of patch testing with 2% eucalyptus oil and 0.34%, who were tested with 5% eucalyptus oil in a later study.^[43,44] Occupational hand dermatitis from eucalyptus oil has occurred among aromatherapy and food industry workers.^[45] Exposure to multiple aromatherapy oils has caused airborne ACD in a patient, who showed a positive patch test from 2% eucalyptus oil.^[46] ACD occurred in a patient from an anti-inflammatory cream with a positive patch test from 1% eucalyptus oil, and another patient developed ACD from eucalyptus oil in Vicks VapoRub[™].^[47,48] Systemic allergic dermatitis occurred from tea tree oil and the patient reacted to 5% eucalyptol.^[49] Botvid et al.^[50] recently reported occupational hand/face dermatitis in two florists due to Eucalyptus cinerea leaves used as greenery in flower arrangements with positive patch tests from leaves and stems "as is" and reviewed other five similar cases reported in the literature. Jojoba oil, a liquid wax ester from the jojoba bush in Mexico, United States, and Israel, is an infrequent contact sensitizer.^[51,52] Juniper oil or the oil of Cade is present in shampoos, deodorants, liniments, disinfectants, and many topical medications. It is mostly an irritant but ACD from occupational exposure occurs sometimes.^[53] Patch testing is recommended using a 50% concentration of commercially available oil of Cade to exclude irritant reactions. Neem oil is extracted from the seed kernels of Azadirachta indica (vernacular Neem) which grows throughout South Asia. More than 140 compounds have been isolated from it, many of them with confirmed biological activity.^[54] Indian Ayurvedic texts mention the medicinal benefits of neem, and all parts of the tree are traditionally considered highly useful for its antibacterial, anti-inflammatory, and antiproliferative activity and have been used as insect repellent,

botanical herbicide, fertilizer, and in herbal medications for topical therapy of several skin disorders.^[55] Although contact sensitivity from neem has been observed frequently, it perhaps remains underreported.[56-59] Hamamoto et al.[60] described a patient with psoriasis who used an herbal medication containing neem oil for topical application and developed dermatitis after about 5 weeks. Patch tests with neem oil (1-10%) were positive. Similarly, another patient of Reutemann and Ehrlich^[61] developed facial dermatitis from 100% neem oil used for treating alopecia areata and a patch test with pure neem oil was positive at day 4 reading. Greenblatt et al.^[62] have also reported ACD from neem oil. Patch testing showed 2+ reaction only to neem oil at day four, while all five control subjects had negative reaction. Recently, a similar case of ACD with a positive patch test (2+ reaction to neem oil at day 3) has been reported from neem oil used for treating atopic dermatitis flare.^[63] Occupational ACD too has occurred in a worker manufacturing natural soaps and creams containing neem oil.[64] Triterpenoid compounds (azadirachtin, nimbin), coumarins, and perhaps some impurities are the possible allergens present in neem oil in varying amounts depending on the extraction process used. Azadirachtin is an irritant in nature and can be removed for dermatological use by treating natural seed oil with alcohol.^[62] Sensitization to *olive oil* is not uncommon, especially when it is used as a vehicle in topical medicaments. Occupational contact dermatitis from olive oil has been reported in masseurs, pedicurists, and pizza makers.^[65,66] A patch test is performed with olive oil "as is" as testing with methyl ester of linoleic acid, the glyceryl trioleate, and the glycerides of arachidic acid, the constituents of olive oil will usually produce negative results. Peppermint oil (menthol) is a common flavoring and cooling agent in mouthwashes, cough syrups, chewing gum, cigarettes or foods and may cause perioral dermatitis, cheilitis or stomatitis. It is also a common constituent of medicated lotions for its cooling and antipruritic effect. It is a rare contact sensitizer and has caused contact dermatitis from cigarettes or a transcutaneous containing peppermint/menthol.^[67-69] Contact patch hypersensitivity from sesamin and sesamolin, the main allergens in sesame oil, is possible and has occurred in a few patients with stasis ulcer following topical use of a mixture of zinc oxide and sesame oil.^[70,71] Tea tree oil (from Melaleuca alternifolia tree) is being used with increasing frequency in many commercially available skin and hair care products for its "natural' antimicrobial properties. Its topical use has been associated with ACD. Airborne contact dermatitis from vapors of tea tree oil has been reported in a patient using tea tree oil for steam inhalation.^[72] ACD, systemic contact dermatitis, erythema multiforme-like reactions, and systemic hypersensitivity reactions have occurred with tea tree oil. The tea tree oil reaction was considered relevant to the presenting dermatitis in 41% of patients from Australia, where tea

tree oil is being used more often.^[73] Patch testing is usually recommended with a 10% concentration of tea tree oil.

NITROGLYCERINE

Contact dermatitis from topical nitroglycerine ointment has been reported but not with systemic or sublingual administration.^[74,75] Occupational contact dermatitis has also occurred in pharmaceutical workers engaged in the manufacturing of nitroglycerine.^[8] Nitroglycerine is now available in transdermal therapeutic system, and adverse cutaneous reactions have been reported in 10–70% of its users, and transient irritant reactions are more frequent than ACD.^[8,76] However, ACD may occur from acrylate adhesive in the transdermal therapeutic system as well. Patch testing with nitroglycerine 0.5% (aq.) or 2% (pet) is recommended to identify allergic cases.^[8]

PETROLATUM

Petrolatum, also known as soft paraffin, petroleum jelly, or Vaseline, is a mixture of semisolid hydrocarbons and is used universally as a patch test vehicle and as a therapeutic agent for the relief of skin inflammation and burning, removal of the scales, crusts, and debris, and providing protection from irritants. It is considered non-sensitizing and non-irritating, and it provides sufficient occlusion for patch testing. The test allergens dissolved in petrolatum also remain allergenic nearly for a year, making it an ideal patch test vehicle. Natural petrolatum is a purified mixture of semisolid hydrocarbons obtained from petroleum and is odorless. The artificial petrolatum is prepared by mixing natural hydrocarbon waxes with refined mineral oils, and the synthetic petrolatum is obtained from the hydrogenation of the synthetic hydrocarbons. White petrolatum is prepared by a prolonged purification process until all of the yellow color is removed. Cases of chronic dermatitis, contact urticaria, and hyperpigmentation from petrolatum intolerance have been reported from either or both yellow and white petrolatum especially when used over damaged skin.^[77-80] The allergens present in petrolatum are mainly polycyclic aromatic hydrocarbons, these are impurities and are among several of the possible allergens.^[81] Since petrolatum is the primary vehicle used in patch testing, petrolatum allergy may present with "angry back" phenomenon and these patients may be misdiagnosed as intolerant to several topicals due to many positive patch test results.^[79,80,82] Synthetic petrolatum being pure is best used as a patch test vehicle. Its reported mild comedogenic properties, especially when used continuously under occlusion for 6 weeks or more also remain contested.^[83]

PROPOLIS

Propolis or bee glue is a resinous product bees mix with wax to form their hives. Beeswax obtained from honeycombs is purified and used in cosmetics and medicinal preparations for its antiseptic and healing properties. Honey alone or after electrospinning with propolis has been also used as a biologic wound dressing to expedite healing due to their antibacterial, antioxidant anti-inflammatory, and properties.[84,85] Occupational contact dermatitis from propolis generally occurs in beekeepers (beekeeper's dermatitis) or workers employed in molding artwork from beeswax.[86,87] Nonoccupational contact dermatitis from propolis occurs and has been reported more often in recent years from its increased use in several medicinal preparations.[88,89] Propolis in ear drops used to treat a child has caused acute eczematous rash over the face and arms of the mother.^[90] Systemic contact dermatitis with generalized involvement from propolis has been reported following transepidermal, subcutaneous, intravenous, intramuscular, or oral exposures.^[91,92] Wanscher^[93] also described two patients who developed stomatitis and perioral dermatitis from chewing natural propolis products. The 3-methyl-2-butenyl caffeate and phenylethyl caffeate are the main contact sensitizers in propolis while flavonoids, beeswax, essential oils, fatty acids, and pollen present in propolis apparently have limited sensitization potential.^[92] Raw unpurified beeswax has contaminants from poplar or other tree resins and is often a cause of contact dermatitis. Whereas, contact sensitivity to honey remains under estimated. Patch testing with propolis 10% in petrolatum is recommended. Cross-reactions can occur with Balsam of Peru (Myroxylon pereirae).

RETINOL

Retinol, a vitamin A derivative, is an antioxidant and a major ingredient of prescription medications (RetinA, Yugard) or OTC cosmetics containing 0.15%, 0.5%, or 1% of retinol palmitate used for skin rejuvenation. It improves elasticity, reduces pigmentation and fine wrinkles by desquamation and hydration of the skin, increases collagen production, elastin, and cell division/turnover. After topical application, it is easily absorbed in the skin and gets converted into its active derivative, retinoic acid, or tretinoin, which is responsible for the anti-aging properties of retinol. Retinol is also frequently combined with alpha hydroxy acids such as glycolic acid or vitamin E (tocopheryl acetate) in anti-aging formulations. Application site skin irritation, redness, dryness, and peeling are common adverse effects of topical retinol. It also increases sun sensitivity and discoloration with sun exposure. Occupational ACD from retinyl acetate has been reported.^[94] There are reports of ACD from retinol palmitate (vitamin A) in a moisturizing cream or otherwise.^[94,95]

SELENIUM SULFIDE

Selenium sulfide (2.5%), an anti-infective agent, is used in shampoos to treat dandruff or seborrhea and pityriasis versicolor caused by different species of *Malassezia*. Selenium disulfide has a bleaching effect on hair and may alter the color of dyed hair or discolor metallic jewelry. Its use should be avoided over broken, inflamed skin and in children. Selenium sulfide shampoo should not be applied two days before or after hair coloring or perming. It is necessary to rinse it thoroughly from the hair before any such hair treatments are carried out. It can cause irritant contact dermatitis or burning pain after prolonged topical application, but no allergic reaction has been reported from it.

SULFUR

Sulfur-containing medications once used for the treatment of scabies still find use in household remedies for anti-pruritic properties. Repeated topical applications of sulfur powder in oil or ointment can cause irritant dermatitis and persistent itching. Allergic contact sensitivity to topical sulfur is reported rarely.^[96]

TACROLIMUS AND PIMECROLIMUS

These topical calcineurin inhibitors belong to the ascomycin class of macrolactam immunosuppressive drugs, have similar pharmacological properties, and have been approved for the treatment of atopic dermatitis. Other "off label" indications for dermatological disorders include vitiligo, lichen planus, psoriasis, and cutaneous lupus erythematosus. Tacrolimus 0.03% is approved for children, and 0.1% concentration is used for adults while pimecrolimus is used as a 1% cream. Topical application is associated with application site erythema, stinging, burning, pruritus, dry skin, and skin infections. Reports of rare cases of skin cancer and lymphoma on continuous long-term use of tacrolimus prompted US FDA to issue "black box" warning that has been contested since then by dermatologists worldwide. ACD from topical tacrolimus has been reported in a 9-year-old boy and patch testing with a 2.5% concentration of tacrolimus was positive.^[97] Similarly, Saitta and Brancaccio^[98] reported ACD from pimecrolimus. In another case, ACD was actually due to the oleyl alcohol constituent in the pimecrolimus cream.^[99]

UREA

Urea is a diamide of carbonic acid and is used alone or in combination with other humectants or keratolytic agents like salicylic acid. It gently dissolves the intercellular matrix and helps desquamate the stratum corneum, thereby softening hyperkeratotic skin. It has been demonstrated that moisturizers containing 3–10% urea reduce transepidermal water loss in atopic and ichthyosis patients. The effect is more pronounced when these are applied on moist skin, thereby improving hydration and barrier function. A paste containing urea up to 40% is used for medical nail avulsion. Topical application is generally well tolerated. Application site stinging, burning, itching, or irritation is usually transient lasting for an hour or so. The irritant effect is enhanced when urea is used under occlusion. Patch testing with urea cream will often produce irritant reactions.^[100]

VITAMIN B5

Vitamin B5 or dexpanthenol, the stable alcoholic analog of pantothenic acid, is found as a component in several OTC products such as sunscreens, hair lotions, shampoos, and some prescription medications. It has been found to have an anti-inflammatory effect. Topical dexpanthenol acts such as a moisturizer, reduces trans-epidermal water loss, and improves symptoms of skin irritation, dryness, roughness, scaling, erosions and fissures, and experimental ultraviolet-induced erythema.^[101] Topical application of dexpanthenol is generally well tolerated, but ACD is also not uncommon.^[102,103] Roberts *et al.*^[104] reported a case of ACD from a facial hydrating lotion containing panthenol and cocamidopropyl PG dimonium chloride phosphate, a phospholipid complex of pure coconut oil.

VITAMIN C

Vitamin C or ascorbic acid has been a commonly used antioxidant in skin-lightening and anti-aging cosmetics in recent years. Being highly unstable, it is chemically modified by esterification of the hydroxyl group, leading to derivatives such as ascorbyl tetraisopalmitate and ascorbyl palmitate. Ascorbyl tetraisopalmitate is lipid soluble and used as an antioxidant, emollient, and skin conditioning agent. Ethyl ascorbic acid or 3-o-ethyl-ascorbic acid, an ether derivative of ascorbic acid, is more stable, lipophilic, and hydrophilic and has better skin absorption than its other derivatives. Although allergic reactions to vitamin C are very rare, urticaria, asthma, or fatal anaphylaxis from intravenous administration has happened.^[105] Facial dermatitis occurred from vitamin C in anti-aging cosmetic cream, and a patch testing with ascorbic acid (5% aq.) and the patient's own cream elicited relevant positive patch test reactions. However, an oral provocation test was negative, and complete healing without relapse occurred after the avoidance of the implicated cream.^[105] Metz et al.^[106] reported a case of systemic contact dermatitis presenting as widespread eczema after oral vitamin C with a positive patch test with pure vitamin C. The patient developed eczema 20 h after oral provocation with 2 g of vitamin C, whereas there was complete resolution of eczema with a vitamin C free diet.

Facial dermatitis from 3-*o*-ethyl-ascorbic acid in antiaging or skin-whitening cosmetics has been reported more often.^[107-110] However, cases of contact allergy caused by ascorbyl tetraisopalmitate-containing creams are not uncommon.^[111,112] Assier *et al*.^[112] reported contact dermatitis involving limbs and trunk from ascorbyl tetraisopalmitate used as an excipient in a cream for the management of atopic dermatitis. A patch test showed a positive reaction to ascorbyl tetraisopalmitate at D4, but dietary vitamin C was well tolerated. Swinnen and Goossens^[111] also reported another case of patch test positive ACD from ascorbyl tetraisopalmitate containing anti-aging cosmetics. There were no cross-reactions with ascorbic acid, ascorbyl palmitate, or isopropyl palmitate. Although positive results from 0.05% to 5% (pet.) have been obtained on D3 and D7, patch testing is usually performed with 3-*o*-ethyl-ascorbic acid, 1–10% (aq.). A repeated open application test or "usage test" with a suspected cosmetic product is a useful additional diagnostic tool.^[111]

VITAMIN E

Vitamin E (alpha-tocopherol-acetate or linoleate) obtained from plant sources such as germ oil or synthetic vitamin E is a major lipid-soluble antioxidant used in cosmetics, and several topical medications to treat burns, wounds and scars, or in combination with A. vera for skin moisturizing after dermabrasion and chemical peel.^[113] Contact urticaria, eczematous dermatitis, and EM-like eruptions are known to be caused by vitamin E. Most of these reactions occur from cosmetics and deodorants.[114,115] Vitamin E-induced ACD was uncommon in a review of published reports.^[116] Baumann and Spencer^[117] reported contact dermatitis in 33% of cases treated with topical vitamin E for cosmetic improvement of scars without any benefit. A positive patch test reaction with 1% tocopherol acetate was produced in a patient with generalized dermatitis from vitamin E in soapy oats lotion.[114]

ZINC PYRITHIONE

Zinc pyrithione (syn: ZPTO or bis (1-hydroxy-2(1H)pyridineselonato-O,S) zinc) was developed in the 1930's as an antibacterial (against Streptococcus and Staphylococcus genera) and antifungal agent. Since then, it has been used to treat seborrheic dermatitis and is an active ingredient, mostly in combination with ketoconazole, in several OTC or onprescription anti-dandruff shampoos. It prevents recurrences of flaking, itching, and irritation associated with dandruff, and its antifungal activity has been attributed to its ability to disrupt fungal membrane transport by blocking the proton pump that energizes the transport mechanism.^[118] Except for rare instances of pustular psoriasis triggered by ACD from zinc pyrithione with a positive patch test, its efficacy as a topical treatment of psoriasis has been documented.[119-122] It is relatively safe except for occasional skin irritation from the products that contain it. Allergic contact sensitivity from zinc pyrithione is rare, and only a few cases have been reported.^[123-126] The reported positive patch test rate of

 Table 1: Risk factors for allergic contact dermatitis to topical medicaments or their ingredients.

Risk factors

- 1. Environmental/genetic factors
- 2. Use over body folds
- 3. Occlusive dressings
- 4. Pre-existing dermatoses-
- Stasis dermatitis/ulcers
- Atopic eczema
- Chronic Hand/Feet eczema
- Eyelid dermatitis
- Otitis externa
- Anogenital dermatoses
- Psoriasis
- Previously damaged skin as from cosmetic procedures
- (chemical peels, laser resurfacing, or dermabrasion)

zinc pyrithione ranges between 0.2% and 1.2%.^[127,128] Most cases of ACD from zinc pyrithione containing shampoos present with application site dermatitis involving the scalp and sometimes the face, neck, shoulders, upper trunk, and hands. The report of photosensitivity dermatitis and actinic reticuloid syndrome following contact dermatitis to zinc pyrithione remains anecdotal.^[124] Zinc pyrithione cross-reacts with piperazine, hydroxyzine hydrochloride, and ethylenediamine hydrochloride derivatives. Patch tests with personal shampoos and available shampoo allergens (fragrance, cocamidopropyl betaine, formaldehyde releasers, propylene glycol, vitamin E, parabens, benzophenones, iodopropynyl butylcarbamate, preservatives, etc.) can be performed.

CONCLUSION

Contact dermatitis to ingredients of topically applied medicaments, cosmetics, or home remedies is not uncommon. Although a significant number of cases of contact dermatitis may be due to topicals, they largely remain unsuspected in clinical practice. A strong clinical suspicion and detailed history of the use of personal care products and cosmetics, including home remedies, are essential for an early diagnosis and should be suspected in anyone who complains of intolerance to a particular product.

Ethical approval

The Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent was not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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