Review Article

Alpha-hydroxyacids and carboxylic acids

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Summary

The carboxylic acids include alpha-hydroxyacids (AHAs), polyhydroxy acids (PHAs), aldobionic acids (ABAs), retinoic acid, vitamin C and azelaic acid. They all have therapeutic actions.

AHAs, PHAs and ABAs are organic hydroxyacids, a group of natural and physiological substances which can modulate skin keratinization and increase biosynthesis of dermal components. Because of these effects, AHAs, PHAs and ABAs are therapeutically effective or beneficial for topical treatment of dry skin, rough skin, acne, rosacea, warts, eczema, psoriasis and skin changes associated with ageing, including wrinkles and photoageing. In addition, PHAs and ABAs, which are antioxidants, are topically beneficial for sensitive or diseased skin and for the prevention of oxidative damage caused by UV radiation.

The vitamin A derivatives, known as retinoids, include three that are found physiologically. Retinoic acid is the most potent of these in promoting proliferation and differentiation of epithelial cells, and in stimulating biosynthesis of collagen I and III. Because of these actions, retinoic acid is therapeutically effective for topical treatment of acne, actinic keratoses and photoaged skin.

Vitamin C, which is L-ascorbic acid and a lactone form of 3-keto-polyhydroxy acid, is a water-soluble antioxidant. Because of this property vitamin C has been promoted for topical prevention of skin damage caused by UV radiation.

Azelaic acid has been shown to normalize keratinization in the follicular infundibulum, exert an antibacterial effect against Propionibacterium acnes and inhibit melanogenesis and so has been used for topical treatment of acne and melasma. The carboxylic acids display similarities and differences in their topical actions and therapeutic applications.

Keywords: ABAs, AHAs, aldobionic acids, alpha-hydroxyacids, azelaic acid, carboxylic acids, PHAs, photodamage, polyhydroxy acids, retinoic acid, vitamin C, wrinkles

Introduction

The term, alpha-hydroxyacids (AHA) was introduced to dermatology for the first time in 1974 when AHAs, a form of hydroxyl carboxylic acids, were found to be topically effective for the severe hyperkeratosis of ichthyosis.[1] Since then, AHAs have been found beneficial for topical treatment of dry skin, rough skin, dandruff, callus, acne, keratoses, warts, wrinkles and photoageing skin.[2–5] Glycolic acid, the smallest AHA, is used in peel solutions by aestheticians and dermatologists in office procedures for topical treatment of various skin conditions including rough skin, acne, mottled and blemished skin and skin ageing.[6–9] Other hydroxyacids include polyhydroxy acids (PHAs), aldobionic acids (ABAs); antioxidant polyhydroxy AHAs, which are gentle and beneficial for sensitive or diseased skin such as rosacea, eczema and psoriasis.[10,11]

Vitamins A and C are natural and physiological substances.[12] Azelaic acid, which is a dicarboxylic acid, has been used for topical treatment of acne and melasma.[13,14]

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Table 1 Alpha-hydroxyacids (AHAs).

Common name	Structure	Known occurrence
Glycolic acid	$CH_2OHCOOH$	Sugar cane
Lactic acid	$CH_3CHOHCOOH$	Tomato, sour milk
Methyllactic acid	$(CH_3)_2COHCOOH$	Mango
Malic acid*†	HOOC CH_2 CHOH COOH	Apple
Tartaric acid*†	HOOC CHOH CHOH COOH	Grape
Citric acid*†	$C(OH)(COOH)$ $(CH_2COOH)_2$	Orange, lemon
Cerebronic acid	$CH_3(CH_2)_{21}CHOHCOOH$	Skin as ceramide
Mandelic acid	C_6H_5 CHOH COOH	
Benzilic acid	$(C_6H_5)_2$ CHOH COOH	

*This α-hydroxyacid is also a β-hydroxyacid due to a second carboxyl group.
†Antioxidant substance.

AHAs, PHAs, ABAs, retinoic acid, vitamin C and azelaic acid have one thing in common; they are all carboxylic acids. This article describes, reviews, discusses and compares the similarities and differences in topical actions and indications for these carboxylic acids.

Alpha-hydroxyacids and beta-hydroxyacids

Alpha-hydroxyacids (AHAs) are carboxylic acids having a hydroxyl group attached to the alpha position of the aliphatic carbon atom. Because 'alpha' denotes the position of the 'hydroxyl group', the preferred term or name is alpha-hydroxyacid.[15]

Many AHAs are physiological or natural substances as shown in Table 1. Among all AHAs, glycolic acid or 2-hydroxyethanoic acid, is the smallest molecule. An AHA can also be a beta-hydroxyacid (BHA) if the AHA contains more than one hydroxyl or carboxyl group. Malic acid, tartaric acid and citric acid are α-hydroxyacids based on one carboxyl group but they are also β-hydroxyacids based on the second carboxyl group, because the hydroxyl group is at the alpha position to one carboxyl group but at the beta position to the second carboxyl group. Cerebronic acid, a 24-carbon AHA, is a constituent of ceramide, which functions as a moisturization and permeability barrier in the stratum corneum.[16,17]

Beta-hydroxyacids (BHAs) are carboxylic acids having a hydroxyl group attached to the beta position of the aliphatic carbon atom. The most common BHA is β-hydroxybutanoic acid. A lipid-soluble BHA is tropic acid, which is 2-phenyl-3-hydroxypropanoic acid. It is erroneous to claim that salicylic acid is a BHA.[18]

Alpha-ketoacid (AKA) is related to AHA in that the hydroxyl group is replaced by a keto group. Pyruvic acid is related to lactic acid in that lactate dehydrogenase in the skin converts each acid to the other one.

Table 2 Polyhydroxy acids (PHAs)*.

Common name	Structure	Known occurrence
Glyceric acid	$HOCH_2$ CHOH COOH	Skin
Pantoic acid	$HOCH_2$ $C(CH_3)_2$ CHOH COOH	In vitamin B_5
Ribonic acid	$HOCH_2$ $(CHOH)_3$ COOH	
Gluconic acid†	$HOCH_2$ $(CHOH)_4$ COOH	Skin
Glucoheptonic acid	$HOCH_2$ $(CHOH)_5$ COOH	
Glucaric acid‡	HOOC $(CHOH)_4$ COOH	
Glucuronic acid§	HOOC $(CHOH)_4$ CHO	Body tissues

*Antioxidant substances, also available as lactones.
†Stereoisomers include galactonic acid.
‡Also known as saccharic acid and saccharolactone. The stereoisomers include galactaric acid, also known as mucic acid.
§Stereoisomers include galacturonic acid and iduronic acid.

Polyhydroxy acids

Polyhydroxy acids (PHAs) are carboxylic acids having multiple hydroxyl groups attached to aliphatic carbon atoms, including at the alpha position, and they are commonly present as the lactone form, such as gluconolactone, derived from gluconic acid.[19] Many PHAs are derived from or are intermediate metabolites of carbohydrates, thus the name of each PHA is adopted from the corresponding carbohydrate. For example, gluconic acid is derived from glucose (Table 2) and has five hydroxyl groups attached to the alpha, beta, gamma, delta and epsilon positions, and may be called α,β,γ,δ,ε-pentahydroxyhexanoic acid.[15]

Aldobionic acids

Aldobionic acid (ABA), also known as bionic acid, consists of one monosaccharide chemically linked through an ether bond to a polyhydroxy acid. The ABA may also be described as an oxidized form of a disaccharide or dimeric carbohydrate, such as lactobionic acid from lactose. The name of an ABA is adopted from its correspondent disaccharide, such as maltobionic acid from maltose. Two common ABAs are lactobionic acid and maltobionic acid. Lactobionic acid consists of galactose chemically linked to gluconic acid, and maltobionic acid consists of glucose chemically linked to gluconic acid.[15]

Physicochemical properties

Most AHAs, BHAs, PHAs and ABAs are water-soluble. Some AHAs and BHAs are also soluble in alcohols, e.g. methyllactic acid, mandelic acid, benzilic acid and tropic

acid. Lactobionic acid and maltobionic acid can bind with water up to 14 and 29% content, respectively, and form a transparent gel matrix.[20] Such a gel matrix is desirable for the protection of inflamed skin and in wound healing.

The acid strength of a carboxylic acid is generally determined by its proton dissociation from the carboxyl group in aqueous solution.[21] Most AHAs, BHAs, PHAs and ABAs are considered to be weak organic acids. When a weak acid is dissolved in water, the aqueous solution should consist of three species: undissociated acid molecules, anions and proton ions. The dissociation constant K_a is defined as, in molar concentration, anion multiplied by proton ion, and divided by undissociated acid, and the acid strength is expressed as pK_a. A substance is a stronger acid if its pK_a number is lower.[22] The acid strength of an AHA may not be related to its potency in modulating keratinization, although its pK_a is crucial in the determination of bioavailability and bioavailable concentration, which are important factors in predicting if the topical formulation is therapeutically effective.[19,22]

An antioxidant is defined as a substance capable of preventing or inhibiting oxidation, of disposing, scavenging or suppressing formation or actions of peroxide, superoxide or free radicals. There are three simple screening methods to determine if a substance is an antioxidant; prevention or retardation of air oxidation of (1) anthralin, (2) hydroquinone, or (3) banana peel.[15]
Based on the above three tests, glycolic acid, lactic acid, methyllactic acid, mandelic acid and benzilic acid are not antioxidants. Malic acid, tartaric acid, citric acid, isocitric acid and most PHAs and ABAs have been found to be antioxidants.

Biochemical relationships

AHAs are related to or formed from amino acids. Many AHAs and PHAs are intermediate products or end metabolites in carbohydrate metabolism. Citric acid, isocitric acid and malic acid are important intermediates in the citrate cycle for energy production. Gluconic acid and gluconolactone are important intermediates in the pentose phosphate pathway. Glucuronic acid, galacturonic acid and iduronic acid are the basic components for the synthesis of glycosaminoglycans (GAGs).[23]

There are six different types of GAGs, namely hyaluronic acid, chondroitin sulphate, keratan sulphate I and II, dermatan sulphate, heparin and heparan sulphate.[23] Each GAG is formed from two major carbohydrate components which include PHAs. For example, glucuronic acid is one of the two major components of hyaluronic acid, chondroitin sulphate and heparan sulphate. Iduronic acid is an important component of dermatan sulphate and heparin. Whereas AHAs have been shown to stimulate and increase biosynthesis of GAGs, some PHAs in fact constitute the major components of GAG molecules. These indicate the intimate relationship between AHAs, PHAs and GAGs.

Bioavailability and bioavailable concentration

The stratum corneum consists of keratin-enriched corneocytes which are embedded in a lipid matrix and are very resistant to penetration by ionic compounds or large molecules. Whereas undissociated glycolic acid or lactic acid molecules can readily penetrate into the stratum corneum, the ionized glycolate or lactate anions from a metallic salt cannot.[19] A formulation containing an AHA without neutralization with an alkali usually has a low pH. Because the pH of the skin surface is approximately 4.2–5.6, cosmetic products containing an AHA are partially neutralized with an alkali to raise the pH to 3.5–4.5. Because glycolic acid and L-lactic acid have pK_a values of 3.83 and 3.86, respectively, such cosmetic products will lose half of their potency when the formulation is partially neutralized to pH 3.8.[19,22]

Topical efficacy of a formulation containing an AHA is proportional to the bioavailable concentration of the AHA in an optimal vehicle.[19] The bioavailable concentration is obtained by multiplying the bioavailability by the initial total concentration of the AHA, and the bioavailability is defined as the ratio or fraction of the undissociated AHA in the formulation.

Molecular complex formulation

A formulation containing a small molecular AHA with a lower pH can provoke sensations of tingling, itching, stinging or irritation when applied to sensitive, atopic, diseased or inflamed skin. Such skin reactions could be due to (a) the lower pH of the formulation and (b) uncontrolled release and fast penetration of the AHA into the skin. The lower pH alone cannot account for the stinging and irritation. The faster penetration of glycolic acid and lactic acid molecules into the skin seems to be the major factor in causing skin stinging or irritation.[24] One approach is to develop control or slow-release formulations, since partial neutralization to raise the pH can lose bioavailable concentration and still provokes skin stinging and irritation.

One control-release formulation is an amphoteric system that is based on intermolecular attractive forces between an AHA and an amphoteric substance. There

are three major attractive forces between an AHA and an amphoteric substance: (a) ionic/ionic, (b) dipolar/ionic and (c) dipolar/dipolar.[24] As an example, when arginine is added to a formulation containing glycolic acid, the molecular complex consists of glycolic free acid, glycolate anion, arginine and arginate ion under the above three attractive forces. After the formulation is topically applied to the skin, glycolic free acid involved with the dipolar/dipolar force will penetrate into the stratum corneum first, followed by the one involved with dipolar/ionic force. As more glycolic acid penetrates into the stratum corneum, the glycolate anion will be converted to glycolic acid because of the equilibrium shift. Thus, the amphoteric system can maintain optimal bioavailable concentration with minimal or no skin irritation.

Topical action

AHAs, PHAs and ABAs on topical application can modulate keratinization and stimulate biosynthesis of GAGs, especially hyaluronic acid and collagen fibres, leading to increased skin thickness, which can be measured by micrometer callipers and also determined by histological analysis.[5,25,26] Although the epidermal thickness is also increased, the major part of the increase in skin thickness is in the dermis. The increased skin thickness is not due to oedema formation because it persists for many weeks to months after the discontinuation of topical application. In contrast, topical application of 5% salicylic acid on human forearms has been found to decrease the skin thickness (to be published). The degree of increased skin thickness varies with individual subjects, and with different AHAs, PHAs and ABAs (Tables 3–5).

Because of these dermal effects, AHAs, PHAs and ABAs have been found to be therapeutically effective for topical treatment of skin changes associated with ageing, including wrinkles, photoageing and photodamaged skin.

Skin peels

Glycolic acid, lactic acid, citric acid and pyruvic acid can be used as skin peels in office procedures. Pyruvic acid 100% liquid is the most potent peel solution, but is not recommended for routine use because of difficulties in controlling the depth of peel. Glycolic acid at 20, 35, 50 and 70% concentrations can be used in the dermatology office as peel solutions for topical treatment of various cosmetic conditions and dermatological indications, including rough skin, acne, keratoses, warts, wrinkles, photoageing and photodamaged skin.[27–29] Citric acid peel is used at 20, 30, 40 and 50% aqueous solutions.

Table 3 Alpha-hydroxyacids (AHAs) increase skin thickness.

AHA	Subject (age & sex)	Duration* (months)	Increase over control (%)†
Glycolic acid 10% Lotion	73M	5	11
	58F	8	22
	77F	4	30
	59F	4	43
Lactic acid 10% Lotion	69F	5	17
	59F	6	31
	69M	7	34
	70M	5	42
Methyllactic acid 20% Lotion	76F	1	14
	67F	2	16
	65F	3	20
Mandelic acid 30% Solution	55F	4	22
	62F	4	27
Benzilic acid 35% Solution	68F	6	22
	72M	6	45

*Twice daily topical application on forearm skin.
†Opposite forearm.

Table 4 Citric acid (which is both an AHA and a BHA) increases skin thickness.

Subject (age & sex)	Duration* (months)	Increase over control (%)†
57F	8	7
53F	6	8
52F	6	9
74F	6	11
75F	5	13
72F	7	16
50F	9	19
51F	8	19
76F	5	23
75F	5	26
75F	5	27
70F	5	41
83M	5	55

*20–25% lotion twice daily topical application on forearm skin.
†Opposite forearm.

Lactic acid 90% solution and glycolic acid 70% solution can provoke epidermolysis on the facial skin after a few minutes, depending on skin types. Blanching of the skin is a clinical sign of epidermolysis and indicates the completion of superficial peeling. The subject may feel mild stinging but degrees of discomfort are mild, and

Table 5 Polyhydroxy acid (PHA) and aldobionic acid (ABA) increase skin thickness.

PHA/ABA	Concentration (%)	Subject (age & sex)	Duration* (months)	Increase over control (%)†
Gluconolactone	20	62F	2	7
	20	70F	3	12
	20	79F	2	13
	20	81F	7	17
	20	79F	4	18
	20	72F	2	19
Lactobionic acid	10	63F	4	5
	20	61F	4	10
	22	56F	4	12
	10	64F	5	12
	22	56F	8	13
	8	76M	3	26
	22	49F	10	58

*Twice daily topical application on forearm skin.
†Opposite forearm.

superficial peeling may be repeated at intervals of one to two weeks or longer to provide optimal effects.[8]

Combination compositions

AHAs, PHAs and ABAs can enhance or amplify pharmacological actions of many topical agents, and such actions are not due to enhanced penetration of the agents. Although the mechanism of the synergistic actions is unknown, it appears to be related with the ability of the hydroxyacids to modulate keratinization and induce biosynthesis of dermal components. Enhanced efficacy has been observed with corticosteroids, hydroquinone, diphenhydramine, 5-fluorouracil, and antifungal agents.[20] It has been suggested that the hydroxyacids can disrupt skin barriers and promote better binding between a topical agent and its receptor molecule, resulting in an enhanced topical effect. The hydroxyacids can also reduce or eliminate drug resistance or unresponsiveness, as well as atrophy and rebound worsening associated with topical corticosteroids.[30]

Biological and biochemical mechanisms of action

Although the receptor molecule(s) for AHAs, PHAs and ABAs have not been identified, some basic requirements for the chemical structure may be discussed as follows. The hydroxyl group must be neutral and not acidic in chemical property, like the one in alcohol but not aromatic phenol (slightly acidic). The carboxyl group must be attached to a non-aromatic carbon, preferably an alkyl chain carbon; an amide or ester form is less effective.

Based on available laboratory and clinical data, hydroxyacids at different concentrations provide the following actions: (a) diminished corneocyte cohesion at a lower level of the stratum corneum, near the stratum compactum in hyperkeratotic conditions; (b) diminished number of desmosomes; (c) reduced epidermal thickness in lamellar ichthyosis; (d) increased epidermal and dermal skin thickness in ageing skin; (e) increased synthesis of GAGs and collagen fibres; and (f) increased activities of dermal dendrocytes.[31] The hydroxyacids do not act on the outer layers of the stratum corneum, nor exert a conventional keratolytic action like that of salicylic acid.

Many biological actions are due to or caused by biochemical reactions.

In the stratum corneum, lamellar lipids contain free cholesterol (25%) and small amount of cholesterol sulphate (less than 5%) along with ceramides (45–50%) and free fatty acids (10–15%).[16] But in hyperkeratotic stratum corneum the bulk of cholesterol is present as cholesterol-3-sulphate.[32,33] Whereas cholesterol is non-ionic, cholesterol-3-sulphate is an ionic compound which may cause stronger inter-corneocyte binding and cohesion, resulting in aggregation and less desquamation. It has been shown in X-linked ichthyosis that the skin is deficient in steroid sulphatase.[34] We may speculate that hydroxyacids activate steroid sulphatase to enhance hydrolysis of cholesterol-3-sulphate to free cholesterol in the skin. It has been shown that AHAs such as glycolic acid, lactic acid and citric acid can activate factor XIIIa transglutaminase enzyme, tumour necrosis factor-α, and stimulate mast cells and dermal dendrocytes.[31]

Cosmetic conditions and dermatological indications

Dry skin and xerosis

AHAs, PHAs and ABAs can modulate desquamation at the levels of the stratum compactum in hyperkeratotic conditions, and such action is beneficial in topical treatment of scaly skin, rough skin and dry skin.[35] In senile xerosis, the stratum corneum appears thickened and defective, based on histological studies.[3] Most cosmetic products for dry skin contain humectants or moisturizers which tend to improve water content or prevent water loss from the stratum corneum. However, humectants and moisturizers alone may not eradicate xerosis or dry skin conditions if the stratum corneum remains defective, as in eczema and psoriasis.

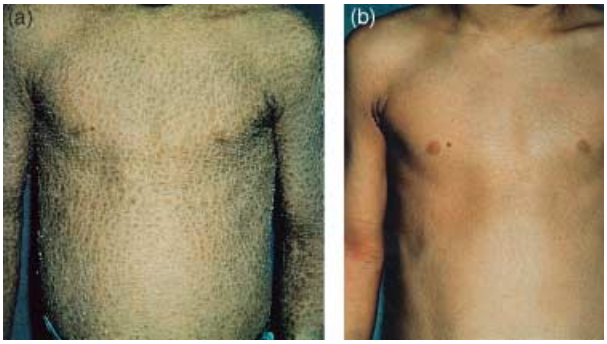

Figure 1 Ichthyosis in a 13-year old. Before (left) and after (right) twice daily topical 10% lactic acid in an oil-in-water emulsion for 3 weeks.

Most AHAs, PHAs and ABAs are not primary humectants. They modulate keratinization; normalizing or improving the quality of the stratum corneum so that water loss is minimized, leading to greater improvement in the dry skin condition.[36] PHA lactones and ABAs are beneficial and gentle to sensitive, diseased or inflamed skin without causing skin stinging and irritation.

Severe dry skin in most cases involve diseased skin such as ichthyosis, eczema and psoriasis, wherein the skin is abnormal, thickened, scaly, fissured and inflamed. The barrier function of the stratum corneum is grossly defective and the skin texture is rough and extremely dry. AHAs such as glycolic acid, lactic acid and mandelic acid at 10% concentration are therapeutically effective for topical treatment of ichthyosis and other severe dry skin conditions (Fig. 1). Gluconolactone 10–15%, alone or in combination with other topical agents, are beneficial and soothing for topical treatment of eczema and psoriasis. Proper combination of several AHAs and PHAs plus antioxidants such as N-acetyl-cysteine in a molecular complex formulation seems to be the most effective for topical treatment of moderate to severe dry skin (Fig. 2).

Acne and rosacea

Since acne lesions initially involve retention of follicular corneocytes, AHAs can be therapeutically effective for topical treatment of acne.[6,37] The best AHAs for acne include glycolic acid, lactic acid, methyllactic acid, mandelic acid and benzilic acid. A combination treatment with alternate use of glycolic acid and retinoic acid formulations provides substantial improvement of acne lesions.[39] AHA peel solutions for severe acne can be used to cause epidermolysis and unroof pustules and beneficially modulate follicular epithelium.[6,38]

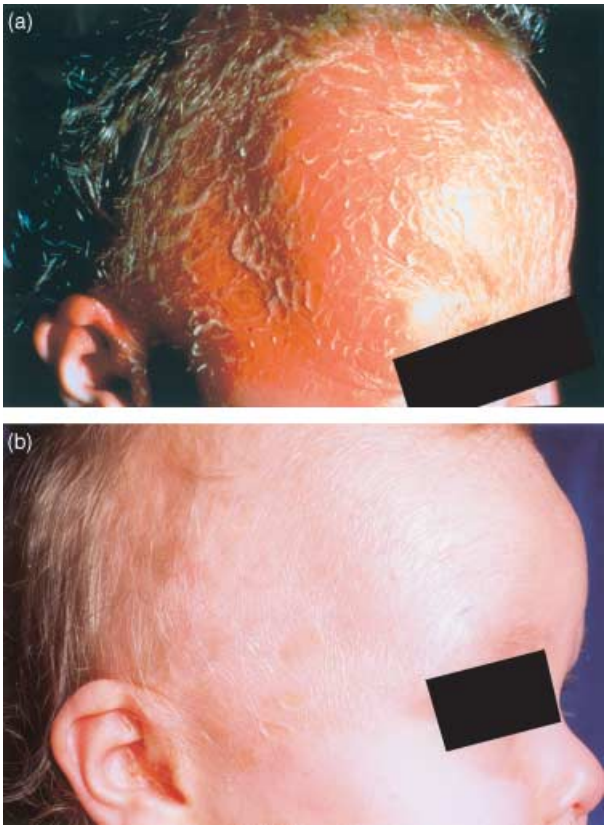

Figure 2 Ichthyosis in a 2-year old. Before (top), showing scaling and erythema, and after (bottom) twice daily topical 8% gluconolactone combination in molecular complex formulation for 4 weeks.

Rosacea is characterized by reactive blood vessels with vascular dilatation or erythema of the face, and prolonged vasodilation can lead to telangiectases. Acne-like papules and pustules frequently accompany these events. Metronidazole 0.75% gel may be beneficial for topical treatment of rosacea, but has no effect on telangiectasia. PHA lactones such as gluconolactone and ribonolactone, are antioxidants and gentle to sensitive skin; in 5–10% creams they are beneficial and effective for topical treatment of rosacea.[10]

Synergistic treatment

A composition containing a pharmaceutical agent in combination with an AHA or PHA has been found to amplify therapeutic potential with less side-effects for various indications including warts, eczema, psoriasis and onychomycosis.[6,20]

For topical treatment of warts, a simple approach is (a) to remove the hyperkeratotic plate by scalpel paring;

(b) for the patient to apply, with a cotton applicator, 0.5% 5-FU in glycolic acid 70% solution twice daily to the centre of the wart, and cover with tape. The above treatment usually results in complete resolution of lesions within 2–4 weeks.[7]

Eczema presents as persistent inflammatory skin lesions with constant or recurrent itch. Ideally, the successful treatment of eczema is immediate eradication of itch followed by clinical improvement of eczematous lesions. A cream formulation containing diphenhydramine free base and a PHA lactone such as gluconolactone can eradicate eczematous itch within a few minutes, followed by clinical improvement of eczematous lesions. Addition of hydrocortisone-17-valerate to such a formulation can quickly induce substantial remissions of nummular eczema and lichen simplex chronicus.[20]

Tachyphylaxis is frequently encountered with corticosteroid for topical treatment of psoriasis. We have discovered that a formulation containing both a corticosteroid and an AHA or PHA lactone, or an alternate use of two separate formulations can prevent or eradicate tachyphylaxis in psoriasis. The above treatment can also prevent rebound worsening, thinning and atrophy of the skin from topical corticosteroids.[15,30]

Because of the hard keratin plate, nail involvements with yeast or fungal infections are usually difficult to treat. When an AHA such as glycolic acid is incorporated into a composition containing an antifungal agent such as clotrimazole, the formulation becomes topically effective, and the improvement of fingernail and toenail infections progresses at the rate of nail growth; approximately 1 mm per week for a fingernail and 0.5 mm per week for a great toenail. In most cases, the fungal infection of a nail is arrested by topical treatment with the synergistic composition containing 2% clotrimazole and 20% glycolic acid.[20]

Cutaneous ageing and photoageing

Skin ageing can be caused by internal or external factors, or both.[40–43] Intrinsic ageing is a physiological degeneration caused by declining ability and functions coinciding with increasing age. Daily topical application of AHAs, PHAs or ABAs in creams or lotions can be beneficial prophylactically as well as in topical treatment.

In contrast to intrinsic ageing, extrinsic ageing is an accelerated degeneration caused by ultraviolet (UV) radiation, ionizing radiation, air pollution, wind, cold, heat, dampness, chemicals, smoke and cigarette smoking. Unprotected, sun-exposed face and hands are typical areas which show extrinsic skin ageing. Photoaged or photoageing skin is rough, dry, mottled, yellowish, leathery, thickened, inelastic, and has various kinds of

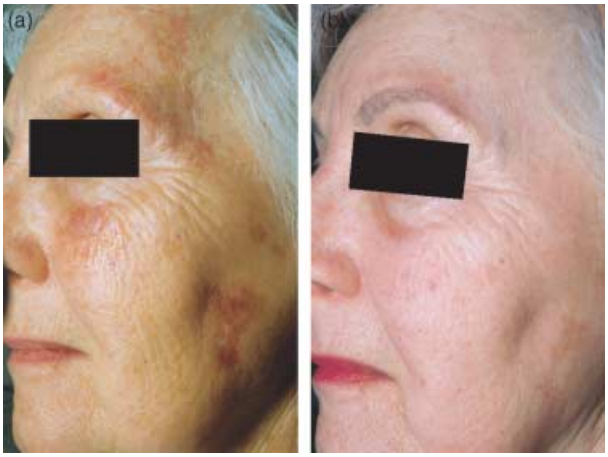

Figure 3 Photodamaged skin, including coarse wrinkles and actinic keratoses, in a 78-year old before (left) and after (right) monthly topical peels with 1% 5-FU in 85% lactic acid and 12% lactic acid cream twice daily for 6 months.

blotches, nodules, keratoses, pigmented spots and deep wrinkles. Intrinsic ageing cannot be arrested, but cutaneous ageing can be modified by topical application of AHAs, PHAs or ABAs to improve appearance and reverse some of the evidence of extrinsic ageing.[44–47]

Keratoses and age spots

With chronic exposure to sunlight, macules and papules which appear on the face and the back of hands include pigmented lentigines, non-pigmented keratoses and actinic keratoses. Actinic keratosis lesions are identified by topical application of 5% 5-FU cream twice daily to affected areas for a few days, and glycolic acid 70% or lactic acid 90% peel solution is applied to the lesions. When the lesions begin to blanch after a few minutes, 0.5–1% 5-FU in 30% glycolic acid solution is applied to the lesions.[7] The above procedure has resulted in complete eradication of actinic keratosis in most cases (Fig. 3).

For eradication of keratoses and age spots, lactic acid 90% or glycolic acid 70% peel solutions can be used as office procedure. The procedure can be repeated at intervals of several weeks, and combined with home treatment with a cream or gel containing 10% AHA with or without 2% hydroquinone (Fig. 4).[7]

Wrinkles and photoageing

AHAs, PHAs and ABAs have been found to be therapeutically effective for topical treatment of wrinkles and photoageing skin because they increase skin thickness by stimulating biosynthesis of hyaluronic acid and collagen

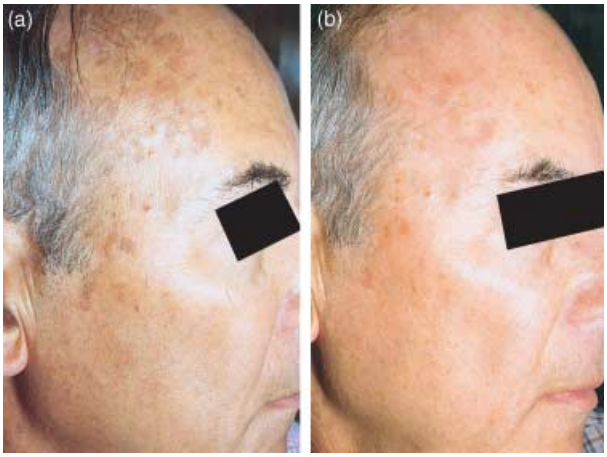

Figure 4 'Age spots', including multiple lesions of seborrhoeic keratoses and lentigines, in a 64-year old, before (left) and after (right) topical 10% glycolic acid and 2% hydroquinone cream twice daily for 9 months.

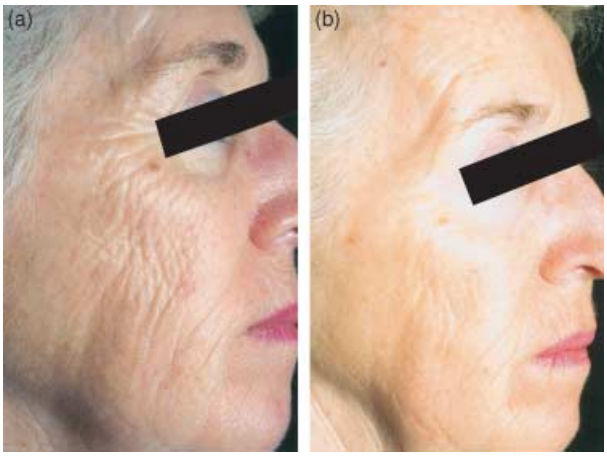

Figure 5 Photoaged skin, with coarse wrinkles, in a 61-year old, before (left) and after (right) 1–2 monthly 70% glycolic acid peels and twice daily 10% glycolic acid cream for 28 months.

fibres. The hydroxyacids at 10–15% concentrations can be used by a patient at home for topical treatment of fine wrinkles on the face. Repeated office procedures using glycolic acid 70% solution, or lactic acid 90% can provide faster improvement and resolution of coarse wrinkles.[6–8,47] The best approach appears to be a combination of peels and sustained home use of a hydroxyacid at 10 to 15% concentrations (Fig. 5).

Antioxidants and ultraviolet radiation

Humans need oxygen for energy and living, and oxidation is essential for survival. During oxidation, reactive oxygen species (ROS) may be produced by peroxidation, and include superoxides, hydrogen peroxide, hydroxyl radicals and peroxyl radicals.[48] The hydroxyl radicals appear to be most reactive and can react with proteins, nucleic acids, lipids and other components to alter their forms and structures, and result in cell and tissue stress. Under normal conditions, endogenous antioxidants and reductive enzymes in the body can dispose of those harmful ROS. These antioxidants and enzymes include vitamin C, vitamin E, reduced glutathione (GSH), reduced α-lipoic acid (thioctic acid), reduced nicotinamide adenine dinucleotide phosphate (NADPH); reduced ubiquinones (coenzyme Q), superoxide dismutase, which converts superoxide to hydrogen peroxide and oxygen, and both catalase and glutathione peroxidase, which convert hydrogen peroxide to water and oxygen.[48–50] Under abnormal or extreme conditions, the amount of these endogenous antioxidants may not be sufficient enough to overcome the increased amount of ROS produced by continued exposure to UV radiation. Typical skin reactions or damage caused by UV radiation include erythema, oedema, exfoliation, tanning, and abnormal thickening of the epidermis; premature signs of extrinsic skin ageing including precancerous lesions.

In addition to sunscreen and sunblock agents, exogenous antioxidants can also be used topically to prevent photodamage. Antioxidants include ascorbic acid, vitamin E, reduced ubiquinones, GSH, L-selenomethionine, flavonoids, tea polyphenols, silymarin, soy isoflavones, reduced lipoic acid and carotenoids. Several AHAs, PHAs and ABAs are also antioxidant substances that can be used as prophylactic treatment to counteract any ROS produced in the skin by UV radiation. Topical antioxidants perhaps should be used routinely in conjunction with sunscreen and sunblock agents to prevent damage induced by UV radiation.

Topical retinoids

Physiological functions and topical actions

Retinoids are based on three basic vitamin A substances: vitamin A alcohol (retinol), vitamin A aldehyde (retinal) and vitamin A acid (retinoic acid). Whereas both retinol and retinal can perform four physiological functions, namely vision, reproduction, growth and differentiation, retinoic acid can perform only the last two functions. Since differentiation is integral to keratinization, vitamin A has therapeutic values for the skin, and on a molar basis the effect on skin keratinization in decreasing order is retinoic acid, retinal and retinol. Vitamin A acid on topical application promotes proliferation and

Table 6 Similarities and differences in topical actions of carboxylic acids*.

Characteristics/Use	AHAs	PHAs	ABAs	RetA	AzA	Vit C
Physiological nutrients or natural substances	+	+	+	+		+
Antioxidants against superoxides/free radicals	†	+	+			+
Gentle to sensitive skin		+	+			+
Gel matrix formation			+			
Constituents of GAGs		+				
Modulate keratinization (helpful for dry skin, acne, keratoses)	+	+	+	+	+	+
Increase dermal components: GAGs, collagen, elastin (helpful for wrinkles, photoageing)	+	+	+	+		+
Increase skin thickness (helpful for wrinkles, photoageing, old skin)	+	+	+			
Synergistic effects with corticosteroids, antifungal agents	+	+	+			
Antibacterial					+	
Melanogenesis inhibitor	?			?	+	

*AHAs, alpha-hydroxyacids; PHAs, polyhydroxy acids; ABAs, aldobionic acids; RetA, retinoic acid; AzA, azelaic acid; Vit C, vitamin C; GAGs, glycosaminoglycans.
†Malic acid, citric acid, tartaric acid and tartronic acid are antioxidants.

differentiation of epithelial cells, and stimulates synthesis of collagen I and III; it is therapeutically effective for topical treatment of acne, actinic keratoses and photoaged skin.[51–55] Two synthetic retinoids, tazarotene and adapalene, which do not have conventional vitamin A structure, have been found to be therapeutically effective for topical treatment of acne.[12] The unwanted side-effects of topical retinoids include dry skin, erythema, pruritus, burning and stinging.

Similarities and differences

Vitamin A, AHAs, PHAs and ABAs can modulate skin keratinization, but their biological and biochemical mechanisms of action are quite different. Whereas vitamin A promotes cell proliferation and differentiation, AHAs, PHAs and ABAs at low concentrations modulate keratinization by diminishing corneocyte cohesion at the stratum compactum in hyperkeratotic conditions. Whereas retinoic acid causes irritation and dry skin on topical application AHAs, PHAs, and ABAs are therapeutically effective for topical treatment of dry skin and ichthyosis (Table 6). Vitamin A acid and aldehyde, AHAs, PHAs and ABAs are therapeutically effective for topical treatment of acne by dislodging comedones from follicular orifices. AHAs at higher concentrations can cause epidermolysis, and can be used as skin peels for topical treatment, but this is not so for retinoids. Vitamin A acid can promote biosynthesis of collagens I and III, and AHAs, PHAs and ABAs can increase skin thickness by stimulating biosynthesis of GAGs and collagen fibres. Therefore, retinoids, AHAs, PHAs and ABAs are all therapeutically effective for topical treatment of wrinkles and photoageing skin, and perhaps should be used together to achieve optimal benefits because of their different paths of performance.

Vitamin C

Physiological functions and topical actions

Vitamin C is L-form ascorbic acid, 3-oxo-L-gulofuranolactone, present in vegetables and various fruits. Vitamin C performs many physiological functions. For example, it promotes wound healing related to hydroxylation of proline and lysine in collagen synthesis and it functions as a water-soluble antioxidant in reducing oxidized vitamin E. Because of its antioxidant and anti-inflammatory effects, vitamin C has been suggested for topical prevention and treatment of photoageing and photodamaged skin.[12,48]

Similarities and differences

Vitamin C is a lactone form of a polyhydroxy ketoacid that is related to PHAs. Both vitamin C and PHAs are antioxidants, but the former is chemically unstable in topical formulations under normal storage conditions.

Azelaic acid

Topical actions

Azelaic acid is a nine-carbon dicarboxylic acid. Azelaic acid 20% cream has been used for topical treatment of acne. It has been suggested that azelaic acid possesses three pharmacological effects, namely (a) a normalizing effect on the disturbed terminal differentiation of keratinocytes in the follicular infundibulum, (b) an antibacterial effect against intrafollicular *Propionibacterium acnes*, and (c) an anti-inflammatory effect in the inhibition of reactive oxygen species.[56,57] Studies have shown that 20% azelaic acid cream may be as effective for acne as 0.05% retinoic acid cream, 5% benzoyl peroxide gel and 2% erythromycin ointment.[13] Azelaic acid 20% cream has been shown to be as effective as 4% hydroquinone for topical treatment of melasma.[14]

Similarities and differences

Whereas azelaic acid exerts an antibacterial effect against *P. acne*, AHAs and PHAs appear to modulate keratinization by diminishing cell cohesion in the follicular orifices. In contrast to AHAs and PHAs, azelaic acid has not been shown to have any beneficial effects on dry skin and wrinkles. Azelaic acid, AHAs and PHAs at higher concentrations appear to diminish hyperpigmentation, although probably by different mechanisms (Table 6).

Discussion

Based on a broad definition, salicylic acid is an aromatic hydroxyacid, and AHAs, PHAs and ABAs are aliphatic hydroxyacids. In contrast to salicylic acid, which effects its keratolytic action from outside inward, aliphatic hydroxyacids appear to exert desquamation at a lower level of the stratum corneum near the stratum compactum. Whereas salicylic acid decreases the skin thickness (unpublished results), aliphatic hydroxyacids stimulate biosynthesis of dermal components and increase the skin thickness on topical application. The difference in topical actions seems entirely due to different chemical structures. Whereas salicylic acid has a hydroxyl and a carboxyl group attached directly to a benzene ring, and the phenolic hydroxyl group is slightly acidic like phenolic, the aliphatic hydroxyacid has the hydroxyl and carboxyl groups attached directly to non-aromatic aliphatic carbons, and the hydroxyl group(s) is neutral in nature. Similarly, vitamin C is a lactone form of a ketoPHA, and is an antioxidant like PHAs and ABAs. However, the topical actions of vitamin C are not the same as those of PHAs or ABAs, because the two hydroxyl groups are acidic.

Biochemical events involved with desquamation are still intriguing. It is known that in normal skin, most cholesterol sulphate is present in the lower levels of the stratum corneum, the stratum compactum, and most free cholesterol is present in the upper levels, the stratum disjunctum. In X-linked ichthyosis, the skin is deficient in steroid sulphatase enzyme. Since cholesterol-3-sulphate is an ionic compound, and free cholesterol has a non-aromatic hydroxyl group and is neutral, the attracting force between corneocytes is greater when the cholesterol is in sulphate form. It can be speculated that aliphatic hydroxyacids may stimulate or activate sterol sulphatase enzyme to hydrolyze cholesterol-3-sulphate to cholesterol.

In topical treatment of photoageing skin, antioxidants such as vitamin C, vitamin E or the like alone seem insufficient to arrest or reverse the ageing process. The candidate substances must possess other specific pharmacological attributes, e.g. stimulating biosynthesis of dermal components, etc. At present, only vitamin A and aliphatic hydroxyacids have been shown to be topically effective for photoageing skin.

In chemical peels using trichloroacetic acid, phenol or the like, the recovery of skin damage depends only on the wound-healing process. In contrast, glycolic acid, lactic acid and citric acid stimulate biosynthesis of GAGs and collagen fibres in the absence of discernible wound-healing process.

Conclusions

Certain carboxylic acids; hydroxyacids, retinoic acid, vitamin C and azelaic acid display some similarities but have distinct differences in their topical actions and therapeutic applications. For topical treatments of various skin conditions ranging from acne, keratoses, and wrinkles to photoageing, best results from AHAs, PHAs and ABAs are achieved with their use as peeling agents, e.g. epidermolysis from glycolic acid, followed by maintenance applications of one or more for restructuring actions on epidermis and dermis.

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