Boring or exciting? A journey through the fatty acid chemistry of the skin

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Fatty acid chemistry plays a major role in our economy. In addition to technical applications and products, fatty acids also play an important role in the food, cosmetics and pharmaceutical industries – close to the skin and body, so to speak. This makes it all the more exciting and interesting to take a look behind the scenes at the synthesis processes of the skin and body.

In addition to water and milk, the first skin care products developed by human civilisation consisted primarily of animal and vegetable fats, oils and waxes. They protected the skin from cold and dehydration as well as from substances and microorganisms in the environment. They also provided the binding agent for skin painting for war and decorative purposes.

Triglycerides – the physiological source of fatty acids

Uses in this original form are practically non-existent today. Instead, skin care products are offered whose actual fat content can only be guessed at from the extensive INCI declaration. The immediate interest in pure fatty substances has been lost – exceptions are their use as massage oils[1] or in baby care.[2] Even for most chemists, fats are, at first glance, an unattractive and overly simple substance to study in detail.
In fact, vegetable and animal fats and oils are basically quite uniform in structure, consisting mainly of triglycerides of long-chain fatty acids (Fig. 1), in addition to a few accompanying substances.

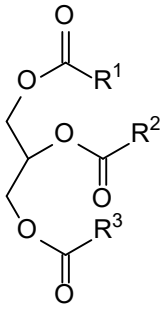

Fig. 1: Structure of triglycerides; R^1, R^2, R^3 = C_mH_n

Like triglycerides, vegetable waxes can be solid or liquid. In addition to other components, they do not contain esters of fatty acids with glycerine, but mostly with longer-chain alcohol components. An example of a liquid wax is jojoba oil, which is extracted from the seeds of the Simmondsia chinensis (jojoba) plant, a shrub native to southern Arizona, southern California and north-western Mexico. A solid animal wax is spermaceti, which is extracted from an organ in the head of whales and consists, among other things, of esters of palmitic acid with hexadecanol and oleyl alcohol.
The properties of triglycerides naturally depend on the character of the fatty acids, whose chain length (m) can vary and whose residues R^1, R^2 and R^3 are saturated or unsaturated. Solid triglycerides are referred to as fats, while liquid ones are referred to as oils.
The body has always been accustomed to dealing with triglycerides. They are physiological components of our metabolism and, when absorbed through the skin or orally, are broken down in the epidermis and by the

[1] H. Lautenschläger, Das sanfte Gleiten – Präparate für die Massage, *Kosmetik International* **2011**, *2*, 36-40.
[2] H. Lautenschläger, Bitte nicht waschen! – Die schonende Hautpflege für Babys und Kleinkinder, *Kosmetik International* **2014**, *5*, 16-19.

microbiomes of the skin and intestines via di- and monoglycerides into glycerol and the underlying fatty acids (Fig. 2):

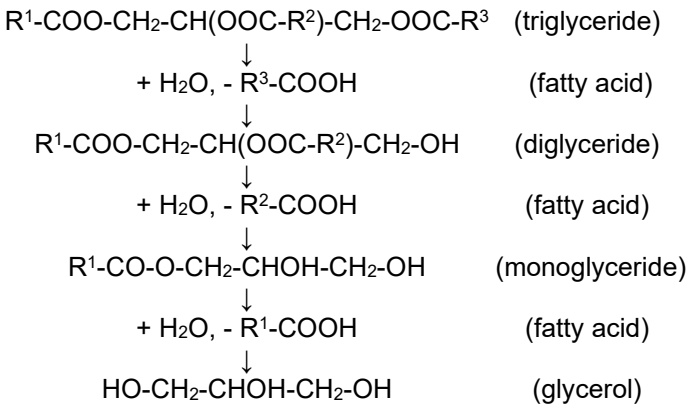

Fig. 2: Enzymatic cleavage of triglycerides into glycerol and fatty acids

While humans have learned to split the triglycerides of vegetable oils and animal fats, initially using soda or potash and later using caustic soda or potash lye in heat, and as intermediate stages quite useful curd soaps (fatty acid sodium salts) and soft soaps (fatty acid potassium salts) were produced as intermediate stages, the breakdown in a physiological environment with the help of enzymes (lipases) proceeds silently and without great energy expenditure. An armada of enzymes ensures the further metabolism of fatty acids.

Nobel Prizes for fatty acid metabolites

Behind the physical fatty acid metabolites lies an extremely complex and challenging biochemistry, which began in 1935 with the discovery of prostaglandins (Fig. 3), culminated in a Nobel Prize in 1982[3] and led to an unprecedented race in the 1970s to synthesise them, including their derivatives and structurally related compounds, with the aim of developing new drugs with separate agonistic or antagonistic effects. The total chemical syntheses of the time and the associated stereoselectivities are still considered masterpieces of organic chemistry today.

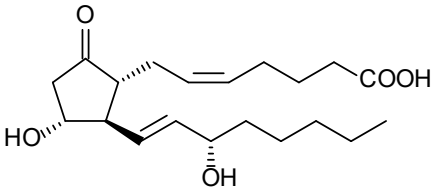

Fig. 3: Prostaglandin E_2 (example)

Biochemically, prostaglandin E_2 (abbreviated: PGE_2; Fig. 3), which is a locally highly effective hormone, ultimately results in the human body from the oral intake of linoleic acid (Fig. 4) and its metabolism.
The double unsaturated linoleic acid (C18:2) occurs mainly in the triglycerides of vegetable oils, for example in sunflower, olive and soybean oil. According to the now widespread opinion, it is one of the less beneficial fatty acids because, to stick with the example, PGE_2 is considered, among other things, to be a mediator for triggering and maintaining inflammation.
However, this is only half the truth, because in addition to PGE_2, other prostaglandins are produced, as well as thromboxanes and leukotrienes, whose individual representatives have diverse, sometimes contradictory local effects on blood vessels, tissues and organs.[4] They are grouped together as eicosanoids, i.e. acids containing 20 carbon atoms. The starting points for prostaglandins and thromboxanes are dihomo-γ-linolenic acid and arachidonic acid – also known as eicosatetraenoic acid (ETA).

[3] The Nobel Prize in Physiology and Medicine in 1982 was awarded to Bengt Ingemar Samuelsson, Sune Karl Bergström and John Robert Vane for their work on prostaglandins and related biologically active substances.
[4] https://en.wikipedia.org/wiki/Prostaglandin

Both acids are formed enzymatically from linoleic acid through dehydrogenation and chain elongation (Fig. 4):

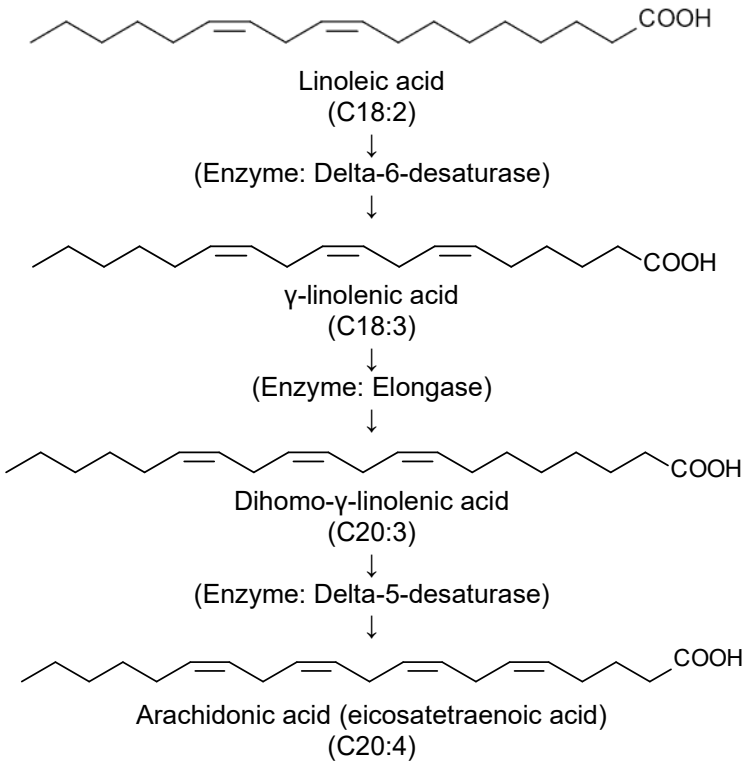

Fig. 4: Formation of arachidonic acid from linoleic acid

With regard to the prostaglandins and thromboxanes formed, the metabolites of dihomo-γ-linolenic acid are referred to as series I and those of arachidonic acid as series II.
Cyclooxygenases bring about oxidation and cyclisation to form the five-membered ring typical of prostaglandins (Fig. 3), which in the case of thromboxanes is subsequently converted into a tetrahydropyran ring (Fig. 5).

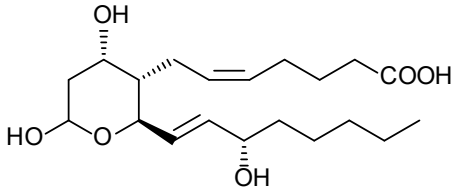

Fig. 5: Thromboxane TXB_2 (example; biologically inactive)

Many non-steroidal anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenases. The best known include aspirin® (acetylsalicylic acid) and ibuprofen (isobutylphenylpropionic acid).
Non-cyclic leukotrienes are produced by oxidation of arachidonic acid with the help of the enzyme 5-lipoxygenase (Fig. 6).

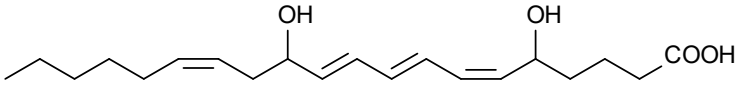

Fig. 6: Leukotriene LTB_4 (example; involved in inflammatory processes)

Skin care with essential fatty acids

Linoleic acid is an essential fatty acid that we absorb through food. The γ-linolenic acid (Fig. 4) produced from linoleic acid is insufficiently produced or not produced at all in a certain percentage of people suffering from neurodermatitis (also known as atopic skin; Fig. 7) due to a delta-6-desaturase deficiency. They benefit from

skin care treatments with evening primrose oil, borage seed oil or hemp oil. These oils contain considerable amounts of γ-linolenic acid bound in triglycerides.

Fig. 7: Atopic skin
(https://de.wikipedia.org/wiki/Atopisches_Ekzem#/media/Datei:Neurodermitis1.jpg; Bernd Untiedt)

Linoleic acid also has an outstanding protective function, as it is incorporated into ceramide I (also known as ceramide EOS) in the skin barrier (stratum corneum) during apoptosis, i.e. the programmed cell death of epidermal cells. (Fig. 8).

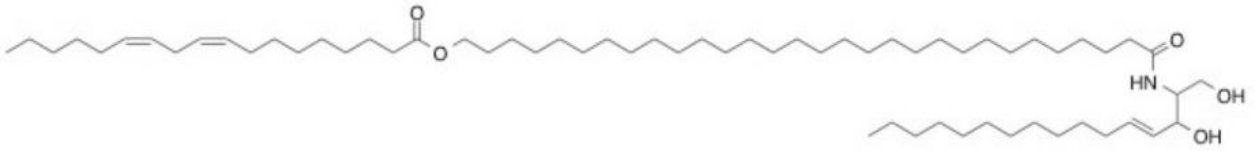

Fig. 8: Ceramide EOS

Ceramide I, together with saturated fatty acids such as palmitic and behenic acid, as well as cholesterol, forms the epidermal lipid bilayers within the skin barrier. The molar ratio of ceramides/cholesterol/long-chain fatty acids is 1 : 0.9 : 0.4.[5,6] The bilayers protect against the penetration of exogenous matter and, conversely, keep transepidermal water loss (TEWL) stable. Ceramide I prevents the skin from becoming cracked and dry and ensures the necessary elasticity of the skin barrier.
To complete the picture of eicosanoids, we must also mention eicosapentaenoic acid (EPA), which is derived from the essential triple unsaturated α-linolenic acid (Fig. 9), and its analogous prostanoid metabolites (series III), which compete in part with series I and II in the body.

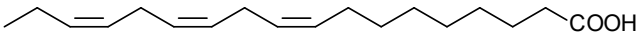

Fig. 9: α-linolenic acid (C18:2)

α-linolenic acid is found in seed oils, such as rosehip, linseed and kiwi, and in single-digit percentages in soy phospholipids (lecithin). Eicosapentaenoic acid (Fig. 10) is also an important component of fish oils. The previously unknown vascular and other diseases that occurred when the Inuit switched from a pure fish diet to a Central European diet are attributed, among other things, to the protective effect of EPA metabolites in this regard. However, many other changes in diet and lifestyle are also likely to have contributed to this.

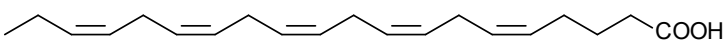

Fig. 10: Eicosapentaenoic acid (C20:5)

[5] I. Plasencia, L. Norlén and L. A. Bagatolli, Direct Visualisation of Lipid Domains in Human Skin Stratum Corneum's Lipid Membranes: Effect of pH and Temperature, *Biophysical Journal* **2007**, *93*, 3142-3155.
[6] L. Norlén, M. Lundborg, C. Wennberg, A. Narangifard and B. Daneholt, The Skin's Barrier: A Cryo-EM Based Overview of its Architecture and Stepwise Formation, *Journal of Investigative Dermatology* **2022**, *142*, 285-292; doi:10.1016/j.jid.2021.06.037.

Essential fatty acids in the diet

Eicosapentaenoic acid (EPA) and its precursors are referred to as ω-3 acids (n-3) because their cis double bonds, each interrupted by a methylene group, begin at the third carbon atom from the end, while arachidonic acid (ETA) and its precursors belong to the ω-6 acids (n-6).
Since ω-3 and ω-6 acids and their metabolites are both present in our organism and, as already indicated, the ω-3 family is considered to be physiologically more valuable, it has been concluded with regard to nutrition that ω-3 acids should be preferred. There is no doubt that this advice is not wrong; however, it completely fails to recognise that the entire physiological metabolism in an organism is characterised by balances. Balances regulate the relationships between metabolites and keep them largely stable. It only becomes critical when the (possibly incorrect) diet cannot quantitatively compensate for a deficiency. In the case of ω-3 acids, fish oil would be a preferred supplement if there is actually a deficiency. However, with a balanced, non-unilateral diet, deficiencies are not to be expected.

Epidermal metabolites of essential fatty acids

The metabolism of unsaturated ω-3 and ω-6 fatty acids via dihomo-γ-linolenic acid, EPA and ETA and their oxidation by 5-lipoxygenase and cyclooxygenases occurs in endothelial cells and internal organs such as the liver. When absorbed by the epidermis, the acids are also oxidised, usually by 15-lipoxygenase (15-LOX):

- 15-LOX peroxidises linoleic acid (octadeca-9,12-dienoic acid) to 13-hydroperoxy-9,11-octadecadienoic acid (13-HPODE), which is then reduced to the anti-inflammatory 13-hydroxy-9,11-octadecadienoic acid (13-HODE).
- The reaction with 15-LOX proceeds analogously with γ-linolenic acid, from which the anti-inflammatory 13-hydroxy-6,9,11-octadecatrienoic acid (13-HOTrEg) is formed via hydroperoxy-6,9,11-octadecatrienoic acid (13-HPOTrEg).
- α-Linolenic acid is converted by 15-LOX via 13-hydroperoxy-9,11,15-octadecatrienoic acid (13-HPOTrE) to 13-hydroxy-9,11,15-octadecatrienoic acid (13-HOTrE). This explains the strong anti-inflammatory effect of linseed oil, which was once a common ingredient in dressings, especially for burns. α-linolenic acid dominates the fatty acid composition of linseed oil triglycerides, accounting for around 60%. In this respect, linseed oil is surpassed only by kiwi seed oil, which contains > 60%. Kiwi seed oil and rosehip seed oil (25-50% α-linolenic acid) therefore have a similar effect.

Today, these oils are used as aqueous nanodispersions stabilised with phosphatidylcholine (the main component of soy lecithin), which completely lack the unpleasant oily character. They are used to treat various types of skin inflammation, including sunburn. Preparations containing essential fatty acids are best used in the evening.

Peroxide and radical formation

If skin care products containing essential fatty acids are used during the day, intense sunlight must be avoided after application, as otherwise uncontrolled oxidation (autoxidation) will occur on the skin surface, leading to inflammatory skin reactions due to the formation of aggressive peroxides. Among other things, radical chain reactions can occur (Fig. 11):

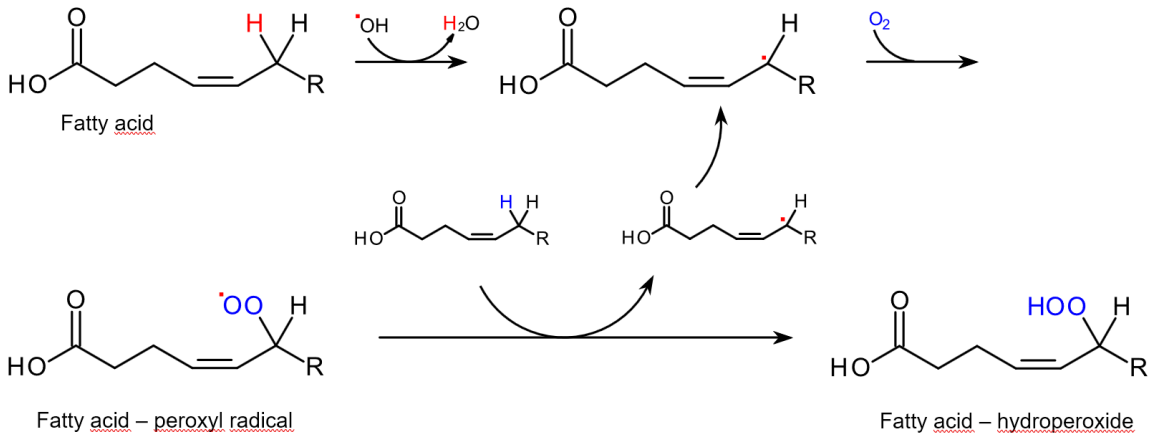

Fig. 11: Radical chain reaction of unsaturated acids under the influence of atmospheric oxygen and radiation

(https://de.wikipedia.org/wiki/Lipidperoxidation#/media/Datei:Mechanismus_der_Lipidperoxidation.svg; Eleska)

The methylene groups adjacent to the double bonds are preferentially attacked, and even more so the methylene groups between two double bonds of polyunsaturated fatty acids.

Preparations containing unsaturated fatty acids can be protected during storage by antioxidants. However, antioxidants are overwhelmed on the skin and under radiation, as the unsaturated fatty acids compete with the antioxidants. An additional factor on the skin is traces of heavy metals, especially iron ions, which form radicals from hydroperoxides and catalyse auto-oxidation with them (Fig. 12).

$$Fe^{2+} + ROOH \rightarrow Fe^{3+} + RO\cdot + OH^-$$
$$Fe^{3+} + ROOH \rightarrow RO_2\cdot + H^+ + Fe^{2+}$$

Fig. 12: Radical formation due to traces of iron (R = H, alkyl)

Heavy metal ions are usually inactivated by additive complexing agents such as EDTA, phosphates, citrates, etc.
Due to the sensitivity of polyunsaturated acids to atmospheric oxygen, oils such as linseed oil and kiwi seed oil are also referred to as drying oils. Linseed oil in particular was used in the past as a varnish for the effective impregnation of wood in outdoor areas. Cobalt salts were usually added to the varnish as a catalyst to accelerate the polymerisation process (resinification) that occurs under the influence of light.
This process is still used today in the manufacture of lubricant additives, whereby the native oils are exposed to a stream of atmospheric oxygen in reaction vessels ("oil blowing"). The onset of oxidation, polymerisation and cross-linking causes significant heating, which can lead to spontaneous combustion in improperly disposed textiles contaminated with linseed oil, for example. Oil painting also continues to use drying oils in combination with pigments.
Pure highly unsaturated oils are valuable foodstuffs, but have a limited shelf life, as autoxidation becomes noticeable even in extremely low concentrations due to the formation of odour- and taste-intensive fatty acid cleavage products. Linoleic acid, for example, produces the saturated aldehydes pentanal, hexanal and heptanal, as well as particularly odour-intensive unsaturated aldehydes such as 2-nonenal and the ketone 1-octen-3-one.

Monounsaturated fatty acids

Monounsaturated fatty acids are significantly less sensitive to oxygen than essential fatty acids, particularly with regard to the double bond to the α-position methylene group. Oleic acid (C18:1 n-9) is the most prominent representative, occurring most frequently in vegetable oils such as olive oil (Fig. 13).

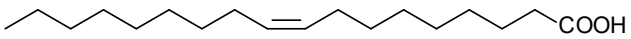

Fig. 13: Oleic acid (C18:1)

It belongs to the ω-9 acids, is an important component of body fat deposits and is therefore mainly used for energy production. In cases of deficiency, oleic acid can also be biosynthesised from stearic acid. One of the metabolites of oleic acid formed by enzymes is eicosatrienoic acid (C20:3 n-9). It is mainly formed when there is a deficiency of linoleic acid.[7] Biophysical factors are thought to play a decisive role in this process.
Oleic acid is often used as a penetration enhancer in topical pharmaceutical preparations. The reason for this is its incorporation into the lipid bilayers of the skin barrier and the associated reduction in its phase transition temperature. While oleic acid integrates into the fatty acids of the skin barrier bilayer, in penetration-enhancing, cell-like liposomes it is native phosphatidylcholine with its high linoleic acid content that behaves like a bilayer and lowers the phase transition temperature of the skin barrier bilayer.[8] Linoleic acid would be even more effective than oleic acid as a penetration enhancer, but is not used due to its instability towards O_2/radiation.

[7] W. O. Lundberg, The Significance of cis, cis, cis 5,8,11-Eicosatrienoic Acid in Essential Fatty Acid. Deficiency, *Nutrition Reviews* **1980**, *38* (7), 233–235; https://doi.org/10.1111/j.1753-4887.1980.tb05910.x.
[8] H. Lautenschläger, Die Haut und ihre Pflege – Physiologie und Chemie im Einklang? *Chemie in unserer Zeit* **2021**, *55* (5), 306-319.

For the same reason, liposomes with native phosphatidylcholine have not become established in topical pharmaceutical preparations.
Similar to double bonds, branches in fatty acids have a physical effect on their esters. Their consistency is usually liquid and their viscosity is low compared to unbranched esters with the same molar mass. This also applies to the respective alcohol components. Branched fatty acid esters of mono- and dicarboxylic acids are therefore preferred as excipients in topical medicines and cosmetics to make them easier to spread on the skin. They are also referred to as spreaders (example: Fig. 14).

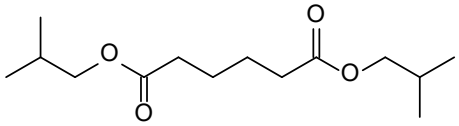

Fig. 14: Diisopropyl adipate is an effective spreading agent

Saturated fatty acids

Fatty acids absorbed from animal and plant foods are stored in the human body as triglycerides or in phospholipids, from which they are enzymatically released and metabolised as needed. Saturated fatty acids, such as palmitic acid (Fig. 15), are mainly used for energy production.

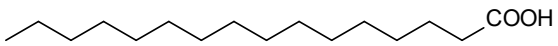

Fig. 15: Palmitic acid (C16:0)

They are preferentially broken down by β-oxidation of the alkyl chain in the mitochondria and ultimately enter the citric acid cycle in the form of an acetyl group (fatty acids with an even number of C atoms), where oxidation to carbon dioxide and water takes place (Fig. 16).

CH_3-$(CH_2)_n$-COOH >>> β-oxidation >>> CH_3-CO-enzyme residue >>> Citric acid cycle >>> CO_2 + H_2O

Fig. 16: Breakdown of saturated fatty acids

In fatty acids with an odd number of carbon atoms, a propionyl group remains at the end of β-oxidation, which is bound to coenzyme A, carboxylated to D-methylmalonyl-CoA and, after epimerisation and isomerisation, enters the citric acid cycle as succinyl-CoA.

Saturated fatty acids that are important for the skin barrier, such as palmitic acid (C16:0), stearic acid (C18:0), behenic acid (C22:0) and lignoceric acid (C24:0), are found in higher concentrations in some vegetable oils such as avocado, macadamia and peanut oil, which are therefore considered to be particularly nourishing. Saturated fatty acids and their esters have the advantage in skin care products and foodstuffs that they are not sensitive to oxygen and can therefore be stored for long periods.
With regard to energy production, the commonly held view that essential fatty acids are preferable to saturated fatty acids is also put into perspective here. Provided that one's diet is not unbalanced, varying ratios of saturated to unsaturated fatty acids in food intake do not play a significant role – unless one consumes too much.

Lipids and fatty acids on the skin's surface

One component of the skin's surface lipid film is sebaceous gland secretion, which includes tri- and diglycerides such as 1-palmitoyl-2-oleyl-3-linoleyl-glycerol, 1,3-dipalmitoyl-2-oleyl-glycerol, and 1,2-dioleoylglycerol[9], wax and cholesterol esters, and the unsaturated hydrocarbon squalene. The lauryl ester of palmitoleic acid (C16:1 n-7) is an example of a wax ester. Contrary to earlier assumptions, the secretion does not contain any free fatty acids when it leaves the glands.[10] Free fatty acids such as sapienic acid (16:1 n-10) at around 25% and

[9] E. Camera, M. Ludovici, M. Galante, J. Sinagra and M. Picardo, Comprehensive analysis of the major lipid classes in sebum by rapid resolution high-performance liquid chromatography and electrospray mass spectrometry, *Journal of Lipid Research* **2010**, *51* (11), 3377-3388.
[10] C.L. Fischer and PW Wertz, *Skin Microbiome Handbook: From Basic Research to Product Development*, Chapter 11: Effects of endogenous lipids on the skin microbiome, Wiley Online Library, 14 August **2020**.

sebaleic acid (18:2 n-10) are apparently only produced in the hair follicles by lipases in the microbiome. The sebum secreted by the hair follicles contains[11]:

- 30–50% glycerides,
- 15–30% free fatty acids,
- 26–30% wax esters,
- 12% squalene,
- 3–6% cholesterol esters,
- 1.5–2.5% cholesterol

and strengthens the protection provided by the skin barrier. Some free acids, such as sapienic acid, have antimicrobial properties. The consistency of sebum allows it to flow freely to the skin's surface. The comedones that develop in acne are usually the result of blockages and inflammation of the sebaceous glands (Fig. 17). This easily explains why skin care products rich in linoleic acid are beneficial, on the one hand due to their influence on the consistency of sebum and on the other hand due to the anti-inflammatory metabolites formed with the help of 15-lipoxygenase. This obviously also applies when linoleic acid is bound as a glyceride, as in native phosphatidylcholine.[12]

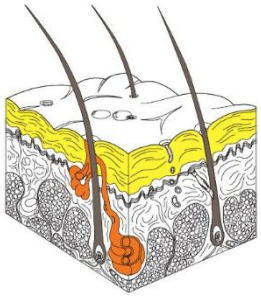

Fig. 17: Cross-section of the skin with stratum corneum (yellow), sebaceous glands (reddish) and hair root

Skin care products with high proportions of saturated fatty acids such as stearic acid ("stearate creams") prove to be counterproductive. In these cases, we refer to comedogenic components, whereby the concentrations, and perhaps even the physical precipitation of stearic acid, are decisive. The extent to which the fatty acid composition of the diet also plays a role in acne can be assumed, but has not yet been conclusively proven.
The long-chain fatty acids of the skin barrier and sebaceous glands, as well as the short- and medium-chain acids of sweat (pH approx. 4.5), such as lactic, acetic, propionic (C3:0), caproic (C6:0) and caprylic acid (C8:0), are components of the acid mantle on the skin's surface[13]. The skin microbiome also contributes to restoring the average pH of around 5.5, for example after cleansing, by splitting glycerides and shortening the chain length of released fatty acids through oxidative degradation.[14] This results in the formation of propionic acid and lauric acid (C12:0), among others. The spectrum of fatty acids changes with age.[15] An important function of the skin surface film and its acids is its antimicrobial activity[16] and thus the resilience of the resident skin flora.
The skin surface acts as a weak buffer. This leads to rapid adjustment in the case of skin care products that have a pH value deviating from pH 5.5 ("pH skin neutral"), such as pH 7 ("pH neutral"). Conversely, if the skin care product is more strongly buffered, even small deviations above pH 7 can lead to barrier disorders. The same problem occurs when the skin is constantly in contact with buffered industrial fluids, such as cooling lubricants. The aforementioned curd soaps (fatty acid sodium salts) and soft soaps (fatty acid potassium salts)

[11] M. Picardo, M. Ottaviani, E. Camera and A. Mastrofrancesco, Sebaceous gland lipids, *Dermatoendocrinol.* **2009**, *1* (2), 68–71.
[12] M. Ghyczy, H-P. Nissen, H. Biltz, The treatment of acne vulgaris by phosphatidylcholine from soybeans, with a high content of linoleic acid. *J Appl Cosmetol* **1996**, *14*, 137-145.
[13] P. Kumar and A. Das, Acid mantle: What we need to know, *Indian Journal of Dermatology, Venereology and Leprology* **2023**, *89* (5), 729-732.
[14] H. Park et al., Pilot Study on the Forehead Skin Microbiome and Short Chain Fatty Acids Depending on the SC Functional Index in Korean Cohorts, *Microorganisms* **2021**, *9* (11), 2216.
[15] B. Howard et al., Ageing-associated changes in the adult human skin microbiome and the host factors that affect skin microbiome composition, *Journal of Investigative Dermatology* **2022**, *142*, (7), 1934-1946.
[16] C.L. Fischer et al., The roles of cutaneous lipids in host defence, Molecular and Cell Biology of Lipids, *Biochimica et Biophysica Acta* (BBA) **2014**, *1841* (3), 319-322.

are also harmful to the skin barrier due to their high pH and high concentrations. Low doses, on the other hand, can be very helpful in hard water, as they render hardness components such as calcium sulphate and calcium hydrogen carbonate harmless by precipitating the fatty acid calcium soaps, thereby softening the water. This is particularly beneficial for people with atopic skin, which is characterised by a disturbed barrier and reduced resistance to microorganisms, among other things.
Fatty acid salts are anionic emulsifiers that were once used both for skin cleansing and in skin care products to stabilise oil-in-water emulsions (O/W). They have long since fallen out of favour due to the pH problems described above and their sensitivity to hard water. One alternative, for example, is the esterification of fatty acids with sugar alcohols (Fig. 18).

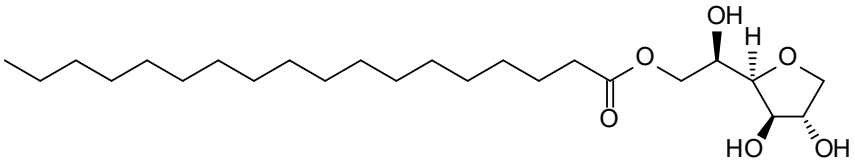

Fig. 18: Sorbitan monostearate

Sugar surfactants, which include esters and glycosides, are used as emulsifiers in skin care products and, in some cases, in foodstuffs, provided that only physiologically compatible fragments are produced during degradation, as in the present case.

Storage of fatty acids

Similar to plants and their seeds, fatty acids serve as energy reserves and are stored in animal organisms as triglycerides. A certain proportion of unsaturated acids (see above: oleic acid) is necessary to maintain a liquid to semi-solid consistency, especially in the presence of long-chain saturated fatty acids. In cells, triglycerides are found in vacuoles, i.e. distributed in fine droplets. In human skin, they are stored in fatty tissue.
A certain lifestyle can lead to larger fat deposits, which, especially in women, increasingly lead to the appearance of cellulite ("orange peel skin"). Cosmetic measures against fat deposits are generally of little effect, even if advertising sometimes suggests otherwise.

Fig. 19: "Orange peel skin"
(https://en.wikipedia.org/wiki/Cellulite#/media/File:Dimpled_appearance_of_cellulite.jpg; tata_aka_T)

In order to mobilise stored fats for energy production, triglycerides in the body are broken down by lipases into glycerol and free fatty acids, which then enter the bloodstream. This process, known as lipolysis, can be stimulated by ultrasound or shock waves and enhanced by injecting aqueous solutions containing phosphatidylcholine and bile acids such as deoxycholic acid ("fat-away injection"). Phosphatidylcholine liposomes loaded with caffeine, which are intended to stimulate microcirculation, are sometimes used topically. Here, too, an additional external mechanical stimulus is necessary to achieve a measurable effect.[17]
The storage of fatty acids in phospholipids, the most important building blocks of the membranes (lipid bilayers) of plant and animal cells, is significant (Fig. 20).

[17] H. Lautenschläger, Cellulite von A bis Z, *Kosmetische Praxis* **2011**, *1*, 10-13 and **2011**, *2*, 10-12.

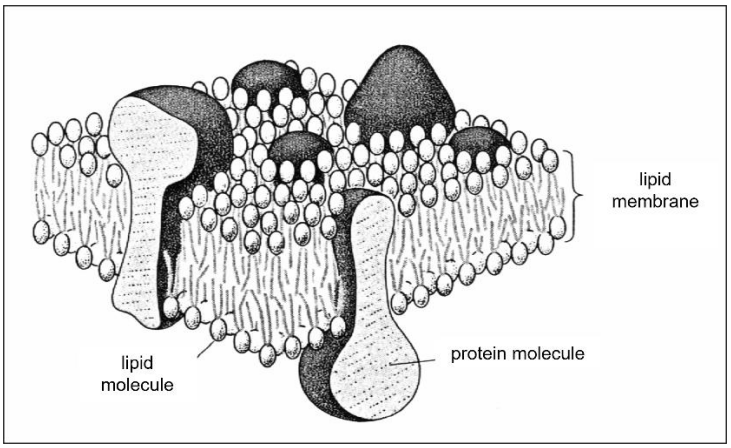

Fig. 20: Section of a cell membrane[18]

The longer-chain metabolites of essential fatty acids such as ETA, EPA and docosapentaenoic acid (produced from EPA by the enzyme elongase) are particularly important here. When needed, they are released by phospholipases, preferably phospholipase A_2, from the 2-position of the glycerol moiety of phosphatidylcholine (Fig. 21) and can have a local hormone-like effect through their metabolites as described above.

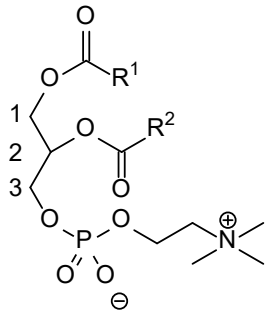

Fig. 21: Phosphatidylcholine (R^1, R^2: fatty acid residues)

Medicines containing glucocorticoids inhibit phospholipase A_2 and thus also the release of arachidonic acid. Corresponding metabolites such as pro-inflammatory prostaglandins (see above) are then not formed.

Hydrogenation of fatty acids

The hydrogenation of unsaturated fatty acids or their triglycerides opens up the possibility of producing products of similar consistency from vegetable oils as an alternative to solid animal fats. Products of this type are widely used in technical areas and in the food industry.
For example, castor oil or ricinoleic acid produced from it by saponification is hydrogenated using Ni catalysts and hydrogen. The reaction product, 12-hydroxystearic acid, is an effective lubricant after conversion to its calcium salt. In skin care, the acid is used as an additive in lipsticks because it helps the product adhere to the skin.
For a long time, margarine was produced by partially hydrogenating vegetable oils. This gave it a consistency similar to that of animal butter. However, this process also led to an increase in the formation of trans fatty acids, which are not present in the original vegetable oils. Trans fatty acids are suspected of influencing lipid metabolism. For this reason, partial hydrogenation has been replaced by full hydrogenation, and the fully hydrogenated reaction products are mixed with the original oils. This has the advantage that the end products contain essential fatty acids.
Incidentally, milk and dairy products such as butter and cheese also contain trans fatty acids, which are produced by microorganisms in the digestive tract of ruminants. These are mainly trans-hexadecenoic acid, also known as trans-vaccenic acid (Fig. 22). The trans double bond is located in the 11th position, counted from the carboxyl group.

[18] B. Alberts et al., *Molekularbiologie der Zelle*, VCH-Verlagsgesellschaft, 2nd edition **1990**.

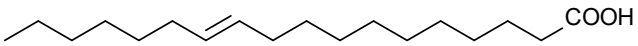

Fig. 22: Trans-vaccenic acid

Trans fatty acids are also produced during deep-frying and when vegetable oils are exposed to high temperatures or during refining processes.

Conclusion

Fatty acids are anything but boring. Their metabolites open up exciting chapters in biochemistry and biology, open up fields of activity in pharmacy and medicine, and present synthetic chemists with major challenges. The links between skin and fatty acids are little known to the general public.

Summary

Fatty acids are characterised by a wide variety of structures and properties. Their functions and the effects of their metabolites in and on the skin are correspondingly diverse. They range from physical protection to local hormonal effects. In addition to the biochemistry of fatty acids in the epidermis, synergistic influences of the skin microbiome play a major role in physiologically intact skin.

Keywords

Fatty acids, triglycerides, eicosanoids, skin barrier, skin microbiome

Terms and abbreviations

Acne: Enlargement and inflammatory changes in the sebaceous glands and hair follicles.
Apoptosis refers to programmed cell death. Apoptosis is part of the continuous skin renewal process, which takes about 4 weeks.
Atopic skin: Sensitive skin that repeatedly reacts to various endogenous and exogenous factors with episodes of redness, scaling, itching or inflammation – often referred to synonymously as neurodermatitis or atopic eczema.
Auto-oxidation refers to the reaction of a chemical compound with atmospheric oxygen – possibly with the involvement of radiant energy and catalysts in the form of ubiquitous traces of transition metals such as iron ions.
Bilayers are double layers consisting of amphiphilic compounds whose lipophilic ends face inwards and whose hydrophilic residues face outwards. Since the lipid character predominates, they are also referred to as lipid bilayers.
Cellulite: Fat tissue under the skin that gives the skin surface an orange-like structure – often on the thighs.
Ceramides are a diverse family of amides resulting from the acylation of the amino alcohol sphingosine with long-chain, partly functionalised fatty acids. Ceramide I, together with cholesterol and long-chain fatty acids such as palmitic acid, forms the lipid bilayers of the skin barrier.
Cyclooxygenase: This enzyme occurs in two isoforms, COX-1 and COX-2, both of which synthesise prostaglandin H_2 (PGH_2) from arachidonic acid, which is then converted into other prostaglandins and thromboxanes (series II). Corresponding metabolites are produced by the action of cyclooxygenase on dihomo-γ-linolenic acid (series I) and eicosapentaenoic acid (series III).
Delta-5-desaturase is an enzyme that inserts a double bond at the 5 position of a fatty acid, counting from the carboxyl group. It belongs to the class of oxidoreductases.
Delta-6-desaturase: Analogous insertion of a double bond at the 6 position of fatty acids.
EDTA: Ethylenediaminetetraacetic acid (complexing agent).
Elongase is an enzyme that extends the carbon chain of a fatty acid on the carboxyl group side by two methylene groups.
EPA: Eicosapentaenoic acid.
Essential fatty acids: Unsaturated fatty acids that are vital for life and must be obtained from food.
ETA: Eicosatetraenoic acid.
Fat-away injection: Injection solution consisting of phosphatidylcholine, deoxycholic acid and water.
INCI: The declaration according to INCI (International Nomenclature of Cosmetic Ingredients) must be stated on the container, outer packaging or package insert of every cosmetic product in accordance with the Cosmetics Regulation (KVO). The INCI lists all the ingredients in the product.
Comedones occur in open or closed form and are also known as blackheads.

Leukotrienes are formed from arachidonic acid through reaction with 5-lipoxygenase. This group of metabolites is involved in inflammatory processes, among other things.
Lipases, also known as esterases, are enzymes that break down esters into alcohols and carboxylic acids by absorbing water.
Lipolysis: Mobilisation and breakdown of fats into glycerol and fatty acids.
Liposomes are physically and chemically similar to the cells of living organisms in terms of their size and the structure of their double-layered membranes (bilayers). The main component is usually phosphatidylcholine, which is obtained from soy lecithin.
Lipoxygenases transfer two oxygen atoms to polyunsaturated fatty acids.
Microbiome refers to the population of microorganisms on or in an organ such as the skin or intestine.
Nanodispersions are liquids containing nanoparticles. A distinction is made between solid and liquid nanoparticles.[19] Liquid nanoparticles based on phosphatidylcholine are readily biodegradable and are often similar in size to liposomes.
Neurodermatitis: See atopic skin.
NSAID: Non-steroidal anti-inflammatory drug.
Occlusivity: Occlusive skin care products or corresponding topical medicines form a surface film on the skin that is impermeable to water vapour and oxygen and has properties similar to those of medical adhesive tape (plaster).
Penetration enhancers are individual substances or bodies such as liposomes or nanoparticles that facilitate the penetration of substances into the skin. Permeation refers to when substances reach the inside of the body through the skin.
Phase transition temperature: The epidermal lipid bilayers contain saturated fatty acids, among other things, and form different phases depending on the temperature. The transition point from the impermeable lamellar gel phase, which predominates at 35 °C, to a more permeable phase is lowered in a concentration-dependent manner by the incorporation of unsaturated fatty acids.
Phospholipase A_2 is an enzyme (esterase) that releases fatty acids bound to the 2-position of the glycerol residue of phospholipids by absorbing water.
Prostacyclin: Another name for prostaglandin I_2.
Prostaglandins: Locally hormone-like metabolites of essential fatty acids.
Sebum is the secretion of the sebaceous glands which, together with the secretions of the sweat glands, forms a lipid film on the surface of the skin.
Spreaders: Mostly branched-chain low-molecular-weight esters that facilitate the horizontal distribution of skin care products on the skin.
Stearate cream: Skin cream whose lipid phase is emulsified and stabilised with alkaline soaps of stearic acid – and, where applicable, palmitic acid.
Sebaceous gland: A gland whose secretion (sebum) flows into the hair canal (follicle), makes the hair supple and spreads over the skin surface after exiting the hair canal.
TEWL: Transepidermal water loss.
Thromboxanes, like prostaglandins, are highly effective metabolites of arachidonic acid.
Triglyceride: ester of glycerol and three fatty acids.
Wax esters: Fatty acid esters of longer-chain alcohols.

What you should know

Fatty acids are multifunctional components that have been used since ancient times from natural sources such as plants and animals. They are synthesised industrially for a wide variety of purposes and play a dominant role in the body's metabolism.
Synthetically and biochemically, the versatility of fatty acids is striking. Their high complexity means that individual aspects are perceived and sometimes one-sided views arise, but a holistic classification is neglected. This applies in particular to the areas of nutrition, medicine and skin care.
All the more so, recent findings in microbiology and dermatology have shown that fatty acids are an important factor in sustainable body care.

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[19] H. Lautenschläger, So klein, so fein - Nanopartikel von fest bis flüssig, *Medical Beauty Forum* **2016**, *2*, 12-16.