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T(r)opical Retinol Alternative with Added Value

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abstract

Retinol has a long tradition in cosmetics as an ingredient for acne-prone skin and in the anti-ageing field. Its effectiveness is undisputed. Retinol is well known and in demand among consumers. Since consumers are showing increasing interest in the ingredients of cosmetics and the trend is moving towards sustainability, more and more natural cosmetic active ingredients are in demand. For retinol, an active ingredient from the tropical plant *Maclura cochinchinensis* comes into question here, which has retinol-like effects and is very mild to the skin. In addition, Maclura extract has other positive properties for the skin that retinol does not have.

Introduction

If you suffered from acne vulgaris as a teenager, you know that you do a lot to at least get through this transition emotionally intact. Blemished skin has a huge impact on quality of life and psychosocial well-being. Getting this under control is not easy and is even associated with strong side effects.

A little over 50 years ago, the US FDA allowed the first topical use of a retinoid, namely tretinoin, for the treatment of acne vulgaris [1]. Tretinoin is the commercial name for retinoic acid (vitamin A acid, all-trans retinoic acid). Over the years, derivatives of retinoic acid have been developed to improve both the stability of the active ingredient and the tolerance of the skin to the active ingredient. In the meantime, the 4th generation of retinoid active substances is available. Strong skin irritations such as itching and redness still occur quite frequently. However, they disappear after a few weeks of consistent use or can be treated well with cortisone. The benefit in acne vulgaris is undisputed and typically the skin disease can be completely treated with retinoids.

Over the years of use, other dermatological applications became apparent, such as treatment of atrophic scars, post-inflammatory hyperpigmentation, photo-damaged skin and melasma. Furthermore, a general "skin rejuvenating" effect was observed.

Since retinoic acid is not permitted in cosmetics due to its high pharmacological effect and the strong side effects to be expected, a precursor of retinoic acid, retinol, is used instead. Retinol, together with retinaldehyde and retinoic acid, belongs to the vitamin A family, which is produced from pro-vitamin A

(or beta-carotene) in our metabolism. Vitamin A is absorbed into the body through food, as are retinyl esters. The cleavage of the ester directly forms retinol, which is further converted to retinal and retinoic acid. To understand the effect of retinol on the skin, we need to look at the biological processes at the cellular level:

In cells, retinoic acid is considerably more effective than retinol [2]. Retinoic acid binds to and activates specific protein receptors on the DNA, the retinoic acid receptors (RAR) and retinoic X receptors (RXR). Eventually, hundreds of specific genes are activated [3]. Activation of these genes is important for reducing the state of acneic skin, but also provides a rejuvenated appearance of the skin. It is believed that for retinol to be biologically effective, it is first converted to retinoic acid. The binding of retinoic acid to its receptor activates numerous genes in keratinocytes, fibroblasts and sebocytes. They control the regulation of sebum, the quality of the horny layer and collagen synthesis. The uniqueness of retinol lies in the fact that it is an anti-ageing molecule with anti-acne properties.

As a versatile, effective concept for ageing and/or acne-prone skin, retinol has a long tradition in cosmetics. Modern consumers like to buy cosmetics with retinol. They are very sensitive to skin health, prefer multifunctional effects and look for substantial active concepts like retinol can offer.

Since the effectiveness of retinol is based at least in part on its conversion into retinoic acid, it is not surprising that undesirable side effects such as skin redness and itching or a disturbed skin barrier may occur during use. This is preferable

during the day, as retinoic acid can be photosensitising. Retinol is therefore often preferred in cosmetics that are applied in the evening or together with a suitable sun protection factor. However, it must be clearly stated that the irritation potential of topically applied retinol is significantly lower compared to retinoic acid.

As consumers increasingly seek milder products that are gentle on the skin barrier, demand for retinol alternatives is on the rise.

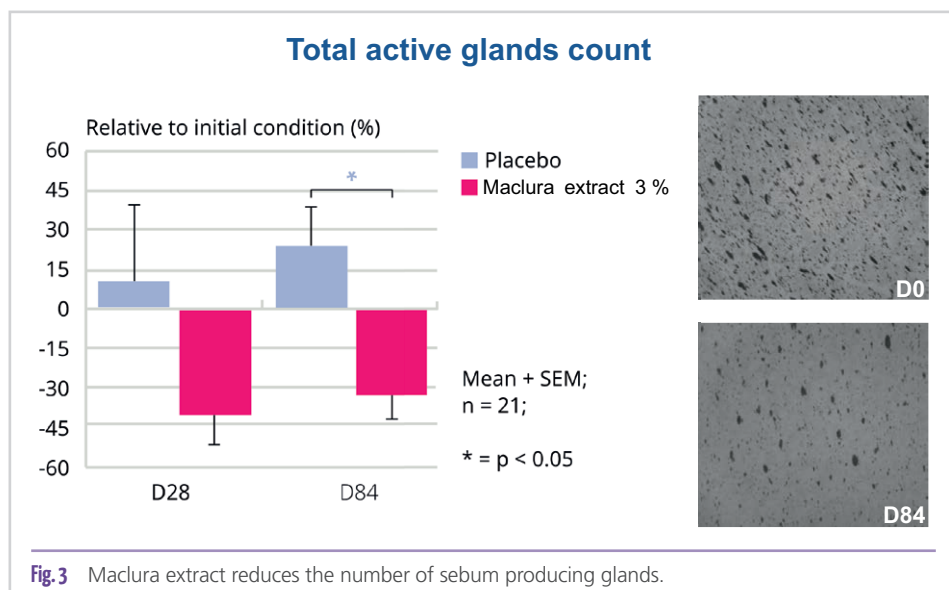
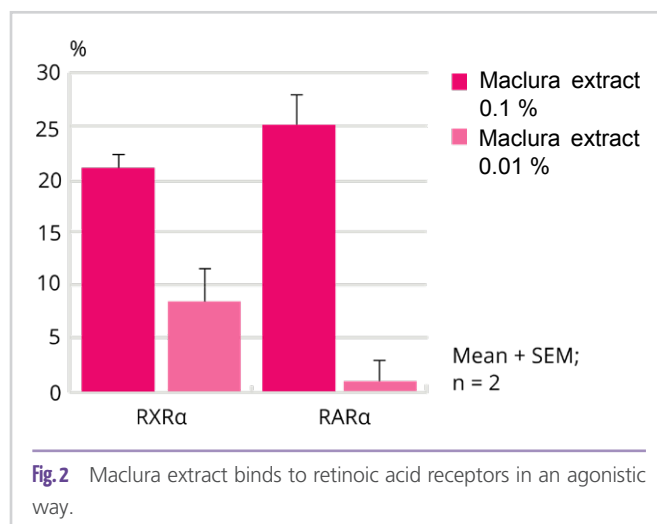
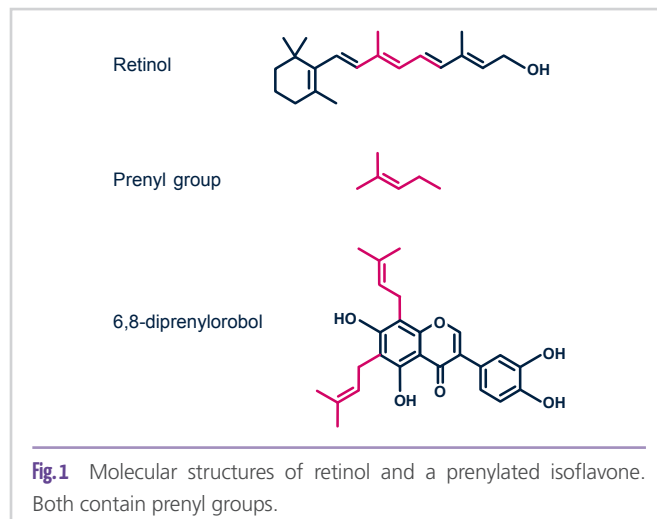
For this purpose, we have to look for substances that on the one hand activate the RAR and RXR receptors, but on the other hand do not trigger skin irritations. After intensive research, RAHN-Cosmetic Actives has succeeded in isolating prenylated isoflavones from the tropical plant *Maclura cochinchinensis* as a valuable retinol alternative (SEBOCLEAR™-MP or Maclura extract, INCI: Propanediol, Bioflavonoids).

Results

At first glance, when looking at the molecular structures of retinol and the prenylated isoflavones, no similarities are apparent. Only, both have prenyl groups. In the case of the isoflavones, they are attached to the aromatic rings as functional groups (**Figure 1**).

Retinol, on the other hand, basically consists of a chain of prenyl residues. It is therefore not to be expected at first that prenylated isoflavones could activate genes with RARE. However, we were able to observe a concentration-dependent, agonistic binding of the prenylated isoflavones to RAR and RXR receptors, which suggests that the corresponding genes can also be activated (**Figure 2**).

When investigating the biological efficacy, it became apparent that sebocytes do not develop to the stage of lipid synthesis when the active ingredient is applied. Instead, they remain stuck in a premature stage (not shown). As a consequence, a reduced sebum production of the sebaceous glands can be expected, which was also confirmed *in vivo* (**Figure 3**). The study with participants having acne-prone skin showed that the application with 3% of Maclura extract



led to a strong decrease in the number of active sebaceous glands already after 28 days.

Reduction of inflammatory spots

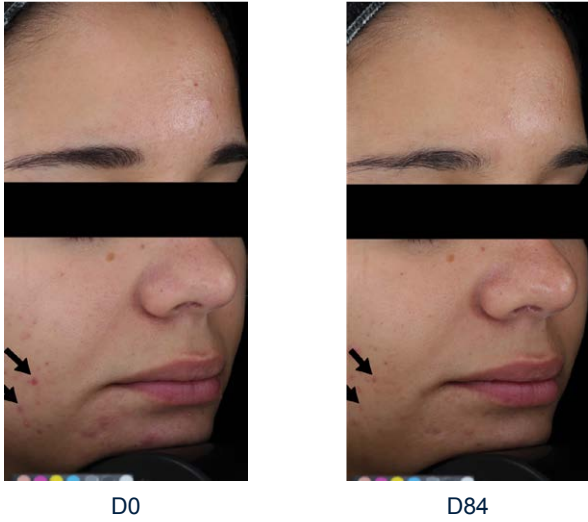


Fig. 4 Maclura extract visibly reduces spots on acne-prone skin.

This resulted in a decrease in porphyrin-positive pores, i.e. *Cutibacterium acnes* infected sebaceous plugs (not shown). There was a clear clearing of the facial skin (Figure 4).

Sebum is produced by the sebocytes located in the sebaceous glands. The released sebum migrates to the surface of the skin. Excess sebum leads to impure and oily skin, promotes the proliferation of *Cutibacterium acnes* and triggers inflammation. Just like retinol, Maclura extract reduces sebum production, which is the first step in controlling oily skin. In addition, Maclura extract even counteracts inflammatory processes and rebalances the skin's disturbed microbiota (Figure 5). It also inhibits the enzyme 5- α -reductase, which is also involved in excessive sebum production, especially in young men (not shown).

Like retinol, Maclura extract activates retinoic acid receptors and has anti-ageing effects. It increases skin firmness and elasticity, reduces wrinkles and improves skin flexibility, evenness and roughness (Figure 6).

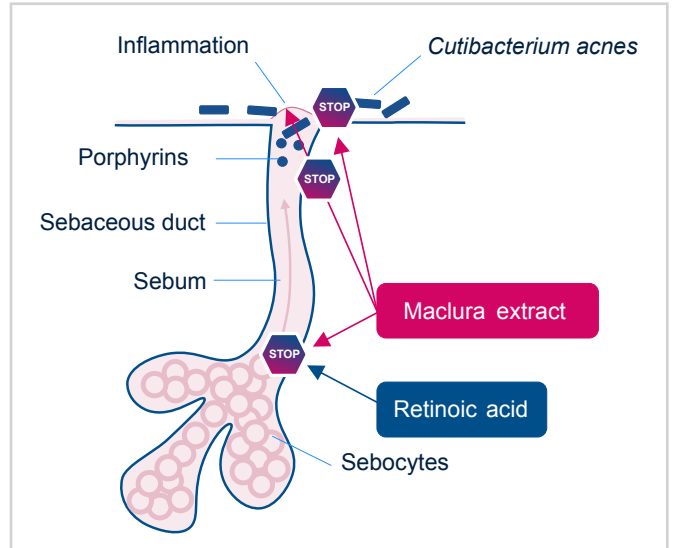


Fig. 5 While retinoic acid's activity is focused on sebum production, maclura extract can address inflammation and *Cutibacterium acnes* as well.

A similar application to effect relationship is shown here as with retinol / retinoic acid. Since the effect is based on a re-programming of the keratinocytes (and sebocytes), a clearly and sustainably improved positive skin appearance only occurs after 4 weeks or later. When using retinoic acid, there is often even a so-called "burst" in the first few weeks, during which the acne worsens. Only after that, there is a visible improvement. This is not the case with Maclura extract. There is no strong "burst" reaction.

Improvements to anti-ageing parameters

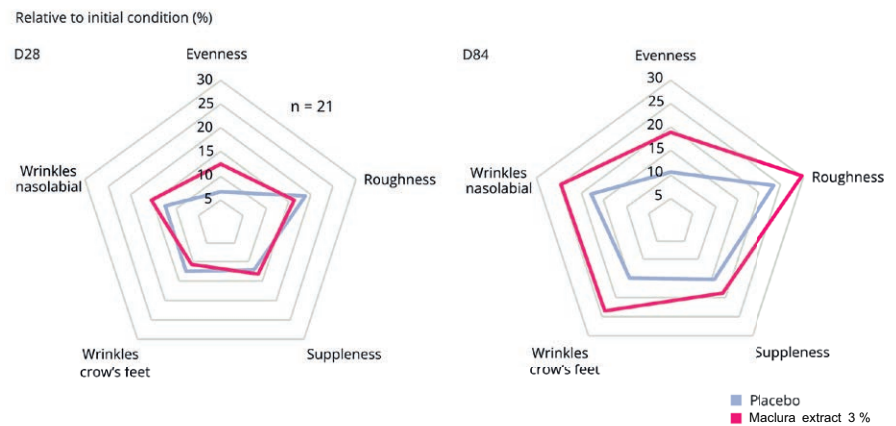


Fig. 6 Maclura extract clearly outperforms placebo in anti-ageing parameters.

Discussion

Maclura extract (SEBOCLEAR™-MP; INCI Propanediol, Bioflavonoids) is the propanediol-based extract from the leaves of the plant *Maclura cochinchinensis*. Only after intensive research, it was possible to specifically isolate three different prenylated isoflavones, including 6,8 diprenylorobol. After exclusion of undesired impurities, a clear, highly active plant extract could be presented. The extract has already been used successfully for several years for acne-prone skin and in the anti-ageing field. Advantages over retinol are as follows: It is a plant-based, water-soluble extract that does not dry out the skin or weaken the skin barrier. Therefore, there is no redness or itchiness with use, or the need to incorporate skin-soothing agents into the formulation to mitigate the irritating potential of retinol. The product is not photosensitive and can therefore be used in day and night cosmetics. Unlike retinol and retinyl esters, it does not have to be converted into an active form by the skin biology. In contrast, it is directly effective and very stable. Furthermore, Maclura extract possesses biological efficacies that retinol lacks: Besides attenuating inflammatory processes (i.e. Maclura extract is already skin-soothing), it acts on 5- α -reductase, a driver of sebum production, as well as *Cutibacterium acnes*, which promotes inflammatory skin processes and the typical acne pimples. Furthermore, it can even be used as a natural deodorant because it slows down the proliferation of corynebacteria in the armpit. The product has received numerous awards. Among others, it received the silver medal at in-cosmetics global 2018 and the bronze medal each at in-cosmetics Asia and Latin America, also in 2018. The product is thus versatile, shows retinol-like efficacy and is a real, natural alternative with the typical RAHN-Cosmetic Actives quality and efficacy.

RAHN-Cosmetic Actives:
Unveiling the secrets of beauty.

Parameter	Retinol	Maclura extract
Activates RAR and RXR receptors	X	X
Delays maturation of sebocytes	X	X
Acts on acne prone skin	X	X
Has anti-ageing efficacy	X	X
Acts on the microbiota		X
Acts anti-inflammatory		X
Inhibits 5-alpha reductase		X
Natural origin	(X) ¹	X
Needs to be converted	X	
Can cause irritation	X	
Can cause "break outs"	X	
Photosensitive	X	
Usable in day and night cosmetics		X
Water soluble		X

¹ Recently, natural retinol qualities became available.

Table 1: Comparison of Retinol with Maclura extract

References:

- [1] Baldwin H, Webster G, Stein Gold L, Callender V, Cook-Bolden FE, Guenin E. 50 Years of Topical Retinoids for Acne: Evolution of Treatment. *Am J Clin Dermatol* 2021, 22: 315-327.
- [2] Repa JJ, Hanson KK, Clagett-Dame M. All-trans-retinol is a ligand for the retinoic acid receptors. *Proc Natl Acad Sci U S A* 1993, 90: 7293-7297.
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