Treatment of actinic keratoses

with a new olibanum extract

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Summary: For the treatment of inflammatory skin diseases and actinic keratosis a new active substance, an olibanum derivative has been discovered. Acetyl-keto-ß-boswellia acid (AKBA) has anti-inflammatory, anti-proliferative and anti-tumorous properties. It is a specific inhibitor of 5-lipogenase - a key enzyme of the inflammatory cascade.

Millions of vacationers deliberately expose themselves to excessive UV radiation. As a result, the risk of UV-related skin damage is rapidly increasing. Sun worshippers thus have to expect an increased risk for actinic keratoses (a carcinoma in situ). Most recent estimates prove that about 8 million Germans suffer from actinic keratoses. There is an estimated prevalence of about 15 percent among individuals over 40 and one out of two of the persons over 60 is affected with such skin lesions.

Actinic keratoses predominantly develop on those parts of the skin which are most exposed to the sun like head, neck, forearms and back of the hands and men even have a higher susceptibility than women. Following excessive UV-radiation, clearly defined red even sometimes scaly patches will develop that may change into white to yellow-brownish crusts. Itching, soreness or disposition for bleeding have only rarely been observed. Most of the actinic keratoses persist as a carcinoma in situ, whereas 20 percent each show spontaneous remission or develop into invasive spino cellular carcinoma. Today, actinic keratosis no longer is classified as precancerous condition but as an early stage of skin cancer.

So far, the standard treatment consisted of cryotherapy and curettage and both the therapies have achieved a 100 percent remission, however, these procedures have also left scars. Another disadvantage is the local treatment as the surrounding skin areas were equally exposed to the sun, but left without treatment. Up to now, topical immune modulators like Imiquimod have only been approved for basal cell carcinomas; they result in remissions of up to 80 percent of the cases and a removal of actinic keratoses without leaving any scars. The therapy may be repeated, but it takes 12 weeks at least and requires high compliance of the patients. The photo dynamic therapy uses light to destroy the tumor cells after they have been photo sensitized with 5-aminolevulinic acid cream. 95 percent of total remissions may be achieved with excellent cosmetic results. The procedure however is quite painful and involves the risk of photo toxic reactions. A therapy of actinic keratoses with Diclofenac gel based on hyaluronic acid shows positive effects. Diclofenac inhibits the prostaglandin synthesis in tumor cells. In 50 percent of the cases the lesions will completely heal and 75 percent of the actinic keratosis patients respond to this specific therapy.

A further and promising active agent has been discovered for the treatment of actinic keratoses. Frankincense extracts and particularly the acetyl-keto-ß-boswellic acid have anti-phlogistic properties and inhibit the 5-lipoxygenase which is a key enzyme of the leukotriene synthesis. Furthermore, the frankincense acid shows anti-proliferative and anti-tumorous effects by inhibiting the topoisomerases and capsases. Frankincense extracts prove highly effective in the treatment of inflammatory and proliferative skin diseases.

Frankincense is a resin gained from desert trees by incising the barks of the species Boswellia serrata, Boswellia carteri, Boswellia sacra, Boswellia frereana or Boswellia papyrifera. The Boswellia trees are mainly grown in the Middle East, above all in Oman, Yemen, Somalia and India. The exuding resin hardens in the sun; it is manually harvested with a special scrape knife and sold at incense bazaars. According to an import company, Europe imported about 700 tons of frank-

incense resins in 2004. Main customer is the cosmetic industry which mainly uses the essential oils.

The use of frankincense for the treatment of various diseases and particularly inflammations and rheumatic joint diseases has been well-known in the oriental folk medicine and above all in India (Ayurveda) and in the countries of the Middle East. As a rule, the resin contains about 5 to 9 percent of frankincense oil, 15 to 17 percent of resin acids, 25 to 30 percent of ether insoluble and 45 to 55 percent of ether soluble compounds. The ether fraction mainly consists of triterpenoid boswellic acids, ß-boswellic acid, acetyl-ß-boswellic acid, 11-keto-boswellic acid and acetyl-11-keto-ß-boswellic acid. Besides the boswellic acids the ether fraction contains essential oils and saccharides such as galactose, arabinose, mannose and xylose. From knowledge of today the boswellic acids are the pharmacologically active agents of frankincense. Sashwati et al. [1] detected the anti-inflammatory and collagen protecting mechanism of the acetyl-keto-boswellic acid. Furthermore, a signal cascade was identified where acetyl-keto-boswellic acid inhibits the expression of matrix metallo-proteinases (MMP), i.e. enzymes which selectively destroy peptide bonds and structural proteins like collagen and connective tissue. Acetyl-keto-boswellic acid significantly inhibits the expression of VCAM and ICAM, the adhesion molecules which participate in infiltrating white blood cells into the inflamed area.

The organism copes with tissue damages by provoking inflammatory reactions as a means to remove the damaging foreign bodies or the damaged tissue parts and to replace them by repair tissue. Hence, inflammation is a physiological process. There are however situations where inflammatory processes may considerably damage organ functions, and in this specific case, the skin functions. Inflammations are biochemically started by the release of so-called inflammation mediators. There are two types of different inflammation mediators which are involved in initiating and maintaining inflammatory processes, viz. prostaglandins and leukotrienes. The current therapy of inflammatory processes consists of medicinal drugs which are able to block the so-called arachidonic acid cascade, i.e. the specific part which contributes to the formation of prostaglandins. The drugs used are part of the steroid and non-steroid anti-phlogistics. Based on this mechanism also is the use of diclofenac for the treatment of actinic keratosis.

The anti-inflammatory effect of the boswellic acids was repeatedly published [2, 3]. By screening the human genome, Sashwati et al analysed the genetic base of the anti-phlogistic effect of boswellia in microvascular endothelial cells and discovered that it inhibits the 5-lipoxygenase, which is a key enzyme for the biosynthesis of leukotrienes. The studies showed that 3-O-acetyl-11-keto-ß-boswellic acid proved to be the most effective 5-lipoxygenase inhibitor among the different boswellic acids. Furthermore, the boswellic acids prevented the TNF-alpha-induced expression of metallo-proteinases. Francincense extracts also prevented the expression of VCAM-1 and ICAM-1. The results of these studies showed that the anti-inflammatory effects of frankincense extracts consisted in influencing the signalling mechanism of the inflammation. Additionally, boswellic acids have cytostatic effects which are based on the inhibition of topoisomerases [4].

It could also be demonstrated that boswellic acids spark off apoptoses [5]. The effects mentioned suggest boswellic acids as an appropriate drug for the treatment of tumors. Ammon and Simmet used boswellic acids for the therapy of brain tumors and found out that both, the brain oedema as well as the tumour mass was reduced. Only recently there have been reports on the chemo preventive and therapeutic effects of acetyl-keto-boswellic acids in the treatment of different types of cancer [6, 7, 8]. In this connection, the boswellic acid-induced inhibition of the topoisomerase-1 and -2 and of the caspase-8 seems to play a significant role [9].

According to the current state of knowledge, the treatment of inflammatory and malignant skin diseases with frankincense extracts or with isolated boswellic acids and their derivatives has not yet been mentioned in the international scientific literature.

For the treatment of actinic keratoses, a standardised frankincense extract containing at least 30 percent of acetyl-keto-boswellic acid has been isolated and embedded in nanoparticles. This active concentrate has been very well absorbed by the skin; it is non-greasing and free of the excessively adhesive properties of the raw extract. The boswellia concentrate was blended into a DMS Cream (Derma Membrane System), (KOKO, Leichlingen) and used for the treatment of actinic keratoses and psoriasis lesions. Additionally, the frankincense extract was added to a vegetable oil mixture and used as a pack for the treatment of the scalp.

First pilot applications have proved that inflammatory and proliferative skin diseases healed relatively fast with the above mentioned therapy. Keratoses and inflammatory reactions could be significantly reduced. These primary results seem to present boswellia extracts as a promising therapy against inflammatory and malignant skin diseases. Further field studies regarding psoriasis and spino cellular carcinoma cases but also inflammatory skin diseases like neurodermatitis and acne have been scheduled.

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