

# Sichuan pepper as a skin "spice"

Christian Artaria<sup>1</sup>, Giada Maramaldi<sup>1</sup>, Giovanni Appendino<sup>2</sup>

<sup>1</sup> Indena SpA., Milan - Italy

<sup>2</sup> Università del Piemonte Orientale, Novara - Italy

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## Summary

*Zanthoxylum bungeanum* Maxim is a perennial plant endemic to the Sichuan province of China. Traditionally, it is employed as a culinary spice for its unique tingling-inducing properties, bound to the presence of a complex mixture of alkaloids, and especially hydroxy- $\alpha$ -sanshool. Alkaloids have a multi-receptor binding profile, being capable to interact with a host of ionotropic- (calcium-, potassium- and sodium type) and metabotropic- (peripheral cannabinoid receptors, CB2) receptors, and are responsible for both the chemesthetic and the analgesic properties of the plant, known as the "toothache tree" for its use in folk dentistry.

Apart from the dietary uses, the pericarps of the seeds of *Z. bungeanum* are the source of an oily extract used in dermatology and in cosmetic formulations to reduce itching and skin discomfort on sensitive and challenged skins. Preclinical and clinical studies have been carried out to elucidate the molecular mechanism of activity of this extract and validate its clinical use in the treatment of itching of various origin. Recently, the lipophilic extract of the pericarp of *Z. bungeanum* has also been reported to exert lifting activity, showing visible and transient improvement of facial wrinkles.

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## Riassunto

Lo *Zanthoxylum bungeanum* Maxim è una pianta perenne endemica della provincia cinese del Sichuan ed il suo frutto privato dei semi (pericarpo), è utilizzato come spezia culinaria per la sua capacità di indurre, grazie ad una complessa miscela di alcalamidi, in particolare l'idrossi- $\alpha$ -sanshoolo, una particolare sensazione di formicolio. Le alcalamidi sono in grado di interagire sia con recettori ionotropici (di tipo calcio-, potassio- e sodio-) che metabotropici (recettori periferici dei cannabinoidi e CB2) e sono responsabili delle proprietà chemestetiche ed analgesiche della pianta, nota anche come "albero del mal di denti" per il suo utilizzo nell'odontoiatria tradizionale. Oltre agli usi alimentari, i pericarpi di *Z. bungeanum* sono la fonte di un estratto oleoso impiegato, in dermatolo-

gia e in prodotti cosmetici, per ridurre la sensazione di prurito e di fastidio su pelli sensibili o danneggiate. Sono stati condotti studi pre-clinici e clinici per indagare il meccanismo d'azione di questi estratti e validarne l'uso clinico nel trattamento del prurito di varia origine. Recentemente è stato dimostrato che l'estratto oleoso del pericarpo di *Z. bungeanum* espleta anche un'attività di lifting immediato, promuovendo un miglioramento visibile e transitorio delle rughe del viso.

## INTRODUCTION

The genus *Zanthoxylum* (Rutaceae family) encompasses at least 250 species (and as much synonyms) endemic to both the Old and the New World.

The Chinese Flora (1) alone describes 41 different species and varieties of this genus.

The botanical subtleties of the genus *Zanthoxylum* are compounded by the broad use of the term Sichuan pepper, that refers to a spice obtained from the fruit husks (pericarps) of various Asian *Zanthoxylum* species, all very similar in terms of colour, size, external surface, as well as sensory properties.

Within these species, *Z. bungeanum* Maxim is the best documented in the Traditional Chinese Medicine, and the Chinese Pharmacopeia (2) reports a specific monograph.

As a medicinal plant, it is employed to reduce the toothache, a use that has gained the plant the attribute of "toothache tree".

*Z. bungeanum* Maxim is popular because of the traditional culinary use of the fruit husks, valued for their aromatic odour and pungent effect, followed next by a sort of numbness on the tongue and the oral cavity, that is deftly exploited in the Chinese and Japanese cuisine to reduce the irritant properties of some foods, and especially hot pepper (3). Despite its pleasant and delicatèd citrus note, *Z. bungeanum* is famous mainly for these chemesthetic properties, variously defined (tingling, paralytic pungency, electricity-mimic) (4). Tingling is a tone totally absent in the Western cuisine, being rather typical of the Far-East culinary tradition, and belongs to realm of chemestesis, namely the food-induced oral somatosensation non mediated by taste- or smell receptors (4).

Familiar chemesthetic sensations are the ones induced by capsaicin from chilly pepper (heat) or menthol from peppermint (cold). Despite

investigations spanning several decades, the molecular mechanism of tingling is still poorly known (4), and might actually be a composite sensation resulting from the stimulation of tactile sensors and the inhibition of sensory nerves function (see *infra*).

Tingling induced by the Sichuan pepper has been related to the presence of unsaturated alkaloids, and especially to a pair of diastereomeric unsaturated amides (hydroxy  $\alpha$ - and  $\beta$ -sanshools, 1a and 1b, respectively) (4), for which a series of specific receptors have recently been identified and cloned. Thus, hydroxy  $\alpha$ -sanshools bind to and inhibit the two-pore potassium channels KCNK3, KCNK9 and KCNK18, a class of pH- and general anesthetics-sensitive ion channels. Hydroxysanshools, as well as other constituents from Sichuan pepper, can also interact with other chemesthetic TRP-receptors, and, therefore, it is not clear to what extent tingling from Sichuan pepper can be traced solely to the interaction of sanshools with two-pore potassium channels alone (5). Sanshools have been recently shown to interact, at least partially, with TRPA1 and TRPV1, and this implication suggests a possible hypothesis for the pungent sensation evoked by Sichuan pepper (6). On the other hand, the interaction with channels of the KCNK type might be involved in the regulation of thermal and physical stimuli in sensory terminals of cutaneous neurons (7).

The soothing sensation induced on the mucous oral membranes has provided a rationale to develop *Z. bungeanum* as a botanical ingredient to soothe sensitive skin. In this condition, the skin is over reactive to external stimuli and environmental factors like temperature variations, UV exposure, and cosmetic detergents (8), and a large share of the population (ca. 60% of women and 40% of men) believes having a sensitive skin and looks for suitable topical products to relief this condition (9).

## FROM SICHUAN PEPPER TO THE COSMETIC INGREDIENT

A lipophilic extract from *Z. bungeanum* Maxim was prepared from the fruit pericarps by extraction and fractionation with CO<sub>2</sub> in hypercritical conditions (10). The process requires the maceration of the fruits and subsequent extraction with CO<sub>2</sub> in continuous recycling for two hours at a temperature of 45°C and a pressure of 250 bar. After CO<sub>2</sub> evaporation the oily fraction is dried under vacuum and standardized to contain 4.4–6.4% of isobutylamides, by dissolving it in about 80% oleyl alcohol. The final product\*, hereafter referred to as Lipophilic CO<sub>2</sub> Extract, is absent of potentially harmful solvent and has been Ecocert® validated.

### Translating ethnopharmacological documentation into scientific evidence

The traditional use of *Z. bungeanum* and preliminary studies demonstrating an interaction of the Lipophilic CO<sub>2</sub> Extract at the neuro-muscular junction served as a basis for a series of studies aimed at defining the functional profile of the product and its use in cosmetic and dermatological products. Thus, the Lipophilic CO<sub>2</sub> Extract has been tested in vitro on the sciatic nerve-musculus extensor digitorum longus pre-

paration of rat to evaluate its effects on synaptic transmission (11).

A Ringer solution with the addition of a detergent was used to improve the solubility of the Lipophilic CO<sub>2</sub> Extract, and a strong, transient action on neuromuscular synaptic transmission (increased frequency of miniature potentials and occurrence of spontaneous plate potentials) was demonstrated. The activation step led to a quick depletion of neurotransmitters, and to a subsequent block of synaptic transmission in a tetrodotoxin (TTX) (1µM) sensitive fashion. This suggested the involvement of voltage-dependent Na<sup>+</sup> channels, since TTX is a specific probe for this end-point, blocking its pore and function, and is in accordance with the effects on sodium and potassium exchanges across the membranes of nerve cells reported for plant alkamides (12). This, and the results obtained in the presence of d-tubocurarine, an antagonist of the nicotinic acetylcholine receptors, suggested a pre-synaptic activity for the Lipophilic CO<sub>2</sub> Extract, and the lack of any direct effect on the muscle (13). These observations are in substantial accordance with the results reported for thermal and tactile sensitivity on hydroxy- $\alpha$ -sanshool (14), and show that alkamides from *Z. bungeanum* are essentially "excitability sensitizers", lacking direct action on muscular activity but affecting sensory receptors as well as neural transmission activity.

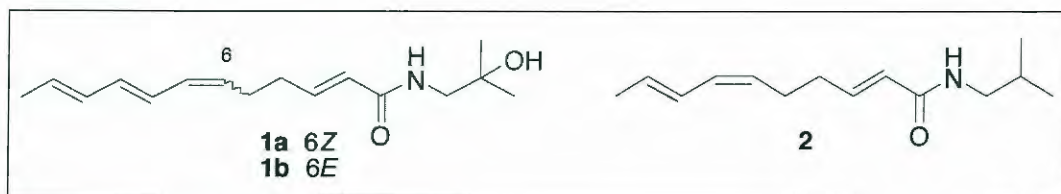


Fig. 1 Hydroxy- $\alpha$ -sanshool and hydroxy- $\beta$ -sanshool.

\* Trade Name: Zanthalene®

## CLINICAL TRIALS

Numerous clinical trials have been carried out to demonstrate the soothing and anti-itching properties of cosmetic and topical formulations containing the Lipophilic CO<sub>2</sub> Extract. Even if itching might be perceived as a minor problem, it might strongly affect social life especially in cases of pathologies of the genital area or strong allergies.

### ***Soothing effect by thermal cutaneous sensitivity***<sup>(13)</sup>

A randomized, double blind study was carried on 12 volunteers, who were trained to define a heat sensation after a thermal stimulus, as "warm", "hot" and "painful" at a certain temperature. A device called Sensitherm®, with a thermal head giving regularly increasing temperature on the skin, was used throughout the experiment. An emulsion containing 0.5% of the Lipophilic CO<sub>2</sub> Extract was applied to the tested area, and a blank emulsion as control. Measurements were taken before the application and 30 minutes after the application of a thermal stimulus. An increase in the sensitivity threshold was observed for 10 out of 12 volunteers. Identification of heat sensation increased by 1.2±0.4°C, warm, as "sensorial comfort", increased by 1.3±0.6°C, hot as "sensorial discomfort", increased by 1.0±0.4°C, whereas the threshold for the definition of the painful sensation did not vary. The observation that the Lipophilic CO<sub>2</sub> Extract affects thermal sensitivity *in vivo* is in apparent contrast with the *in vitro* observation that hydroxy- $\alpha$ -sanshool increases thermal and tactile sensitivity (14), and might be due either to a desensitizing effect (after stimulation the receptor becomes incapable of functioning) or to a prevailing anesthetic effect mediated by the effect of alkamides on sensory nerve function, and, in particular, sodium and potassium exchanges

across the membranes of nerve cells (12).

Remarkably, the pain perception threshold was not affected. Pain receptors or nociceptors are activated by potentially damaging stimuli, and are a heterogenous group of sensors, whose best characterized members are the thermo-TRP receptors (7). Hydroxy- $\alpha$ -sanshool has been reported to increase thermal sensitivity in cultured skin cells (6-8), and the paradoxical results observed on thermal sensitivity in volunteers are presumably the result of a combination of direct sensory stimulation and decreased transmission of neural information.

### ***Soothing effect prior to the application of hair dyes***<sup>(15-16)</sup>

A clinical trial was performed on twenty female volunteers with a specific sensitivity to hair dyes. Their scalp was evaluated by a professional hairdresser prior to the application of the soothing lotion (half of the scalp with a the Lipophilic CO<sub>2</sub> Extract containing lotion at 0.5% and half of the scalp with the blank lotion). Twenty to thirty minutes after the application of the lotion, the hair dye was applied. After dye removal, the hairdresser evaluated the scalp conditions on parameters such as dandruff, irritation, redness, etc., and the volunteers filled in a form describing their scalp discomfort during the hair. Remarkably, 85% of the volunteers chose the the Lipophilic CO<sub>2</sub> Extract - containing lotion when asked to assign a product preference ( $p < 0.0001$ ).

After hair dyeing, all volunteers felt discomfort in the blank treated part, whereas 70% felt no discomfort in the Lipophilic CO<sub>2</sub> Extract treated part and 30% felt "less discomfort" in the Lipophilic CO<sub>2</sub> Extract treated part ( $p = 0.031$ ). The soothing effect appeared earlier with the Lipophilic CO<sub>2</sub> Extract in 80% of the volunteers, with the placebo lotion in 5% of them, while in 15% of the cases no difference was perceived

( $p=0.006$ ). No variation in the scalp or hair conditions was noticed by the hairdresser. Taken together, these observations show that the Lipophilic CO<sub>2</sub> Extract could significantly reduce scalp discomfort in the majority of volunteers, qualifying it as a soothing active ingredient for hair care cosmetic products, like dyes, lotions, or anti-dandruff shampoos.

### **Anti-itching effect after mosquito bites<sup>(17)</sup>**

A spray solution containing the Lipophilic CO<sub>2</sub> Extract at 0.5% was clinically tested to evaluate its tolerability and its soothing and anti-itching efficacy after mosquito bites.

The study involved 40 volunteers who got at least three mosquito (*Aedes aegypti*) bites on each arm. Immediately after the bites, half of the patients treated the bites on their right arm, the other half treated their left arm, with the second arm functioning as control.

The volunteers were required to record the intensity of itching from 1 (very strong itching) to 5 (no itching) and/or pain at 15, 30, 60 minutes and 2, 4 and 24 hours after biting.

Twenty seven out of 40 volunteers (67.5%) reported a positive effect compared to the non treated control arm, whereas no difference was detected by 13 volunteers, showing that the Lipophilic CO<sub>2</sub> Extract could improve the "no itching" and the "weak itching" scores, in particular at short and medium term.

### **Anti-itching effect on atrophic vaginitis<sup>(18)</sup>**

Infections of the feminine genital apparatus like vaginitis and vaginosis are some of the most common gynaecological problems, and, in the majority of cases, are due to bacterial or fungal infections.

The main symptoms are burning, itching and

mucosae inflammation. At least for *Candida* infections, these socially invalidating and discomforting symptoms might be related to the fungal metabolism of the endogenous cannabinoid anandamide, with an overall shift from the "soothing" activation of cannabinoid receptor to "burning" activation of TRPV1, the capsaicin receptor (19). In these conditions, the control of the bacterial infection and inflammation should be associated to a reduction of itching, so as to improve the compliance of the anti-infective therapy. The soothing effect of the Lipophilic CO<sub>2</sub> Extract in atrophic vaginitis was investigated in a clinical study on 15 female patients diagnosed with atrophic vaginitis.

Both objective and subjective symptoms were used as the end-point, and the severity of observed and reported symptoms (itching, burning and dryness in the atrophic vaginitis) was assessed according to the Scott-Huskisson rating scale.

Two multicomponent topical products (a vaginal cream which was associated to an intimate cleanser) containing the Lipophilic CO<sub>2</sub> Extract along with other active (anti-inflammatory and/or antibacterial) ingredients were used. Apart from the Lipophilic CO<sub>2</sub> Extract, the products tested contained standardized extracts from *Glycyrrhiza glabra*, *Matricaria chamomilla*, *Curcuma longa*, and *Malaleuca alternifolia* (Zantogin® Cream and the Zantogin® Detergente from Humana Pharma, Milan, Italy), and were applied twice daily (cream, morning and evening) and used twice daily (detergent) for 10 days.

Controls were taken before the beginning of the treatment, at the end of the ten days' treatment as well as 7 days from the termination of the treatment.

At the end of the treatment, symptoms as itching and burning disappeared in 100% ( $p<0.01$ ) of the patients, whereas the "dryness" parameter decreased by 85% ( $p<0.05$ ) as reported in Table I.

These subjective reports were confirmed by the investigators' objective observation, who found a general improvement in the mucosae conditions compared to the hyperhaemic and hypertrophic state at the beginning of the trial.

Clearly, the multicomponent topical products had effectively counteracted the irritant symptoms typical of the disease, exerting an important anti-itching activity that can be reasonably ascribed to the Lipophilic CO<sub>2</sub> Extract, since none of the other ingredients have been reported to directly affect this end-point. Although the number of patients was small, and the study was limited to a short period of time (10 days), its results were highly statistically significant.

### **Anti-itching and soothing effect in the treatment of psoriasis<sup>(20)</sup>**

Psoriasis is a form of relapsing, non-infective, chronic, autoimmune dermatitis widespread in all human races but more common in Caucasians and most frequent in puberty and menopause.

The main dermatological symptoms are papules and erythematous plaques covered with scales. Although itching is not always present, in some cases it is so evident that it may evolve to more severe forms of dermatological disorders due to the patient's attempt to relieve it.

From a histological standpoint, psoriasis lesions are hyper-proliferative areas with an epidermis

turnover that might be 5 to 10 times faster than normal skin.

In consideration of the significant pro-inflammatory and pro-immune role played by some mediators in the pathogenesis of psoriasis, a multicomponent topical preparation has been developed and clinically tested. The active ingredients of this preparation (Psoribiox® (Montefarmaco OTC, Bollate, Italy) were 18-β-glycyrrhetic acid phytosome®, boswellic acids, the Lipophilic CO<sub>2</sub> Extract, a peptidic-proteic zebrafish egg derivative, and 7-dehydrocholesterol (pro-Vitamin D).

The study was a three-arm study, with twenty patients in each study arm. The patients were treated, respectively with: a) a formulation endowed with antiproliferative activity (calcipotriol), b) a combination of this formulation and a topical product containing a zebrafish eggs extract and 7-dehydrocholesterol, and c) a combination of the calcipotriol formulation and containing 18-β-glycyrrhetic acid Phytosome® (1.0%), boswellic acids (1.5%) and the Lipophilic CO<sub>2</sub> Extract (1%), as well as the peptidic-proteic derivative of zebrafish eggs (0.2%) and 7-dehydrocholesterol (0.005%) also used in Group B.

The study, an open single blind trial, involved a protocol with the applications of the preparations twice daily (morning and evening) for one month.

**TABLE I**

SYMPTOM	T=0	T=10	T=17
Itching	6.2±2.2	0*	0*
Burning	7.1±2.1	0*	0*
Dryness	8.8±1.9	1.6±0.2**	1.4±0.2**

*Symptoms performance (visual analogue scale according to Scott and Huskisson (score 0-10)) on subjects (n = 15) with a diagnosis of atrophic vaginitis before starting the treatment (T=0), after 10 days of applications (T=10) and at day 17th (T=17), 7 days after the last application of the formulations \* p < 0.01. \*\* p < 0.05.*

The response to the different topical treatments was assessed using the visual analogue scale according to Scott&Huskisson's model (clinical scores from 0 to 10 depending on the intensity). This scale evaluates itching, erythema and desquamation.

The parameter of patch extension was objectively assessed through the instrumental measurement of the average of the two (longer and shorter) diameters of a sample consisting of at least 5 patches selected at  $t=0$ . At the end of the treatment, the multicomponent preparation containing the Lipophilic CO<sub>2</sub> Extract (group C) had

reduced itching by 74%, erythema by 73.3%, desquamation by 64.7% and patch extension by 30% (Table II).

The three treatments reduced symptoms and improved each of the considered parameters. While calcipotriol played a major role in the observed improvement, the adjuvant therapy of group C further improved the clinical outcome, reducing itching, erythema and desquamation and slowing down the patch progress. The additional treatment also played a critical role in improving, in group C, the overall tolerability of the calcipotriol treatment.

TABLE II

PARAMETER	GROUP		
	A	B	C
Itching	2.7±0.4*	2.4±0.4*	2.0±0.2**
Erythema	3.0±0.5*	3.0±0.6*	2.0±0.2**
Desquamation	3.3±0.6*	3.2±0.5*	2.3±0.4*
Patch Extension	3.7±1.3	3.5±1.0	3.5±1.2
Efficacy (number of patients)	Excellent (6)	Excellent (6)	Excellent (14)
	Good (10)	Good (10)	Good (6)
	Poor (3)	Poor (4)	Poor (0)
Tolerability (number of patients)	Excellent (0)	Excellent (0)	Excellent (14)
	Good (19)	Good (20)	Good (6)
	Poor (0)	Poor (0)	Poor (0)

Effects of 15-day treatment ( $t=15$ ) on symptoms according to Scott & Huskisson, patch extension (cm ± SD), assessment of treatment efficacy, tolerability and side effects in patients affected by slight/moderate psoriasis.

\* $p<0.05$  vs  $t=0$ ; \*\* $p<0.01$  vs  $t=0$

Treatment: A: calcipotriol; B: calcipotriol and formulation with zebrafish and 7-dehydrocholesterol; C: calcipotriol and multicomponent formulation containing the Lipophilic CO<sub>2</sub> Extract



### Lifting effect<sup>(21)</sup>

the Lipophilic CO<sub>2</sub> Extract has been extensively investigated as a skin-soothing and anti-itching agent (13, 16-18, 20), but due to its activity on voltage dependent Na<sup>+</sup> channels, it could, in principle, also exert lifting activity on the periorcular area. A specific study evaluated the short and long term anti-wrinkle efficacy and the ability of improving skin elasticity of two different creams containing the Lipophilic CO<sub>2</sub> Extract creams (1% and 2%) in comparison to the same emulsion containing a reference product (spilanthol, 2) having similar sensory properties. The investigated formulations had the following composition: Cream A: 2% reference product; Cream B: 2% of the Lipophilic CO<sub>2</sub> Extract; Cream C: 1% of the Lipophilic CO<sub>2</sub> Extract.

Each cream was tested on 14 female volunteers who applied two of the three products (one on each half face) for 4 weeks. Instrumental evaluations of skin roughness by objective measurement of Ra (mean roughness) and Rz (maximum roughness value), were performed at the beginning of the test, after 2 weeks of use and at the end of the test. In order to check the short term efficacy (lifting effect), a double check at 30 minutes after single application both at the basal time and at the final control has been performed. The volunteers were also required to report their evaluation of the products by filling a detailed questionnaire on the efficacy and tolerability of the formulations. The Ra values (medium roughness parameter) of subjects applying the 1% Lipophilic CO<sub>2</sub> Extract cream decreased 30 minutes after the first application from 16.07 ( $\pm$  4.24) to 13.45 ( $\pm$  3.09), and a similar decrease (from 16.47 ( $\pm$  4.34) to 15.26 ( $\pm$  4.7)) was measured also between the last application and the last measurement.

Formulation A and Formulation B did not have any significant effect on the measured parameters.

The Rz parameter showed a decreasing trend from 74.74 to 68.33 ( $\pm$  14.81), although the result was not statistically significant, in the group applying the 1% Lipophilic CO<sub>2</sub> Extract, whilst Formulation A and B did not influence the measured parameter. With products having marked sensory properties, subjective self-evaluations can be biased by emotional feeling, but it is interesting to remark that, while Formulation A was rated as very-to fairly active for an immediate lifting effect by very-to-fairly 85.7% of the volunteers, and Formulation B by 78.6% of them, 100% of the volunteers rated in this way the 1% CO<sub>2</sub> *Zanthoxylum bungeanum* extract. These data are the first demonstration of a lifting activity for hydroxylated alkamides. Although not quite as potent or long-acting as Botulinum toxin, CO<sub>2</sub> *Zanthoxylum bungeanum* extract fully qualifies as a functional cosmetic ingredient for the temporary improvement of skin wrinkles (23).

## CONCLUSIONS

The fruits husks of *Z. bungeanum* (Sichuan pepper) are an important ingredient of the Eastern cuisine. Their unique sensory properties and their use as an anti-itching and lenitive ingredient have stimulated the development of an alkamide-rich lipophilic extract from this spice CO<sub>2</sub> *Zanthoxylum bungeanum* extract as a skin-soothing agent (13, 16-18, 20).

The soothing and anti-itching activity of the Lipophilic CO<sub>2</sub> Extract has been demonstrated in controlled trials, that showed its efficacy as a natural active ingredient for the management of skin discomfort of various origins (itching from mosquito bites, itching due to inflammation or psoriasis, temperature induced skin discomfort, etc.). The thermal sensation (warming, cooling or a combination of both) observed with the Lipophilic CO<sub>2</sub> Extract could be due to activation of specific thermoTRPs (TRPV1 and

TRPA1, respectively), and although Sanshools show only marginal vaniloid activity (6), other constituents of the extract might interact more potently with these end-point or with other thermo-TRPs.

The rationale for investigating the relaxant activity of a shanshool-rich lipophilic extract CO<sub>2</sub> *Zanthoxylum bungeanum* extract on skin superficial muscles was its inhibitory activity against synaptic transmission (11), a type of activity typical of the anti-wrinkle agent Botulinum toxin (Botox®).

Regarding the possible molecular bases for the lifting activity, sanshool could relax subcutaneous muscles with an essentially ionotropic mechanism, related to interaction with sodium channels (tetrodotoxin-like activity), GABA-A receptors (benzodiazepines-like activity), or two-pore potassium channels (general anesthetics-like activity) (6), and studies are underway to elucidate the relative contribution, if any, of these mechanisms to the observed activity.

Even though the molecular mechanism(s) of the culinary and medicinal uses of Sichuan pepper and of the clinical activities of its lipophilic extracts are unclear or even paradoxical in the light of the action on sensory receptors of hydroxy- $\alpha$ -sanshool, the Lipophilic CO<sub>2</sub> Extract represents, nevertheless, a clinically-validated ingredient for the management of skin itching and for the temporary improvement of skin wrinkles.

Improvements in these two conditions can easily be assessed by users, and this has undoubtedly contributed to the success of the Lipophilic CO<sub>2</sub> Extract as a "spice" for the skin.

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### **Author Address:**

Christian Artaria  
Indena SpA.  
Milan - Italy  
Email: christian.artaria@indena.com