

**Allergenic potential of
Arnica-containing
formulations in
Arnica-allergic
patients**

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Contact allergies to *Arnica* are usually attributed to sesquiterpene lactones (SL), which may also have some anti-inflammatory properties (1,2). *Arnica* allergies are either induced by contact with *Arnica* flowers, with other SL-containing Compositae species, or with a particular *Arnica*-containing topical preparation. The question arises whether sensitization to *Arnica* is detectable by a commercially available *Arnica* patch test formulation or it is explained by the SL within it. To address this issue we performed patch tests in patients with a previously documented *Arnica* allergy with commercial *Arnica* patch test preparations, topical pharmaceutical preparations containing *Arnica*, or pure *Arnica*-specific SL.

Materials and Results

The study included eight patients with a previous history of *Arnica* allergy. They had tested positive with a commercial *Arnica* flower extract containing a 0.5% ether extract in pet. (Hermal, Reinbek, Germany) within the previous 2 years. The study was approved by the local ethics committee and conducted according to good clinical practice (GCP) guidelines. The standard *Arnica* patch test was compared to six different *Arnica* preparations, a commercial SL mix (Hermal, Reinbek, Germany), SL freshly isolated from *Arnica montana* flowers (2), and the vehicles as negative controls (Table 1). The commercial products 'Arnica gel' and 'Arnica ointment' from Kneipp are registered as medicines in Germany and their SL content is in a narrow range of 10–15 mg/100 g (0.010–0.015%).

Positive test results could be elicited in five out of eight patients with the commercial *Arnica* patch test (Table 1). Two patients showed no reaction, and three patients showed positive patch tests to 1, 2, or 3 of the other 6 *Arnica* test preparations. One patient reacted positive to every *Arnica* preparation, and two patients displayed a

strong positive reaction to the SL mix. None of the patients testing positive to the standard *Arnica* patch test displayed positive test reactions to the *Arnica*-specific SL. Two patients who tested negative for the standard test but positive for at least one of the *Arnica* ether extracts also showed positive tests to the *Arnica*-specific SL dihydrohelenalin-methacrylate, but not to helenalin-isobutyrate. No positive reactions to the negative controls were observed (Table 1).

Discussion

Arnica flower extract in pet. is widely used as a standard test to identify an allergy to *Arnica*. Although all eight patients included in the study featured a documented positive reaction to this test preparation within 2 years before the study, a positive reaction could only be reproduced in five patients. However, the patients who tested negative for the standard test were positive for one of the *Arnica* ether extracts. This might reflect differences in sensitization, exposure, or variations in the composition of test substances. As shown recently, neither the extraction

Table 1. Patch test results in *Arnica*-allergic subjects (reactions at D3; scoring according to German Contact Dermatitis Research Group)

Patch test substance (test concentration) [producer]		Patients							
		1	2	3	4	5	6	7	8
<i>Arnica</i> extracts	<i>Arnica</i> extract (0.5% SL) [Hermal, Reinbek, Germany] ^a	++	++	IR	++	+++	+	?	–
	<i>Arnica</i> Eastern European ether extract (0.5%) [Kneipp, Würzburg, Germany] ^a	–	?	++	+	–	–	–	–
	<i>Arnica montana</i> cv. Arbo ether extract of flowers (0.5%) [Kneipp, Würzburg, Germany] ^a	–	?	++	+	+	–	+	+
Commercial <i>Arnica</i> preparations	<i>Arnica</i> tincture (25%) [Kneipp, Würzburg, Germany] ^a	–	–	–	++	+	–	+	–
	<i>Arnica</i> gel (0.013% SL) [Kneipp, Würzburg, Germany]	–	+	–	+++	+++	–	+	–
	<i>Arnica</i> ointment (0.013% SL) [Kneipp, Würzburg, Germany]	–	–	–	++	–	–	–	–
	<i>Arnica</i> oil (1%) [Kneipp, Würzburg, Germany] ^a	–	–	–	+	–	–	–	–
SL pure substances	SL Mix (0.1%) [Hermal, Reinbek, Germany] ^a	–	–	–	+++	–	–	–	+++
	Dihydrohelenalin-methacrylate (0.025%) [Kneipp, Würzburg, Germany] ^a	–	–	+	–	–	–	+	–
	Dihydrohelenalin-isobutyrate (0.025%) [Kneipp, Würzburg, Germany] ^a	–	–	–	–	–	–	–	–
	Helenalin-isobutyrate (0.025%) [Kneipp, Würzburg, Germany] ^a	–	–	IR	–	–	–	–	–
Negative controls	Pet. [Kneipp, Würzburg, Germany] ^a	–	–	–	–	–	–	–	–
	<i>Arnica</i> gel vehicle [Kneipp, Würzburg, Germany]	–	–	–	–	–	–	–	–
	<i>Arnica</i> ointment vehicle [Kneipp, Würzburg, Germany]	–	–	–	–	–	–	–	–

^aTest preparations in pet.

SL, sesquiterpene lactones; Score:–, negative; ?, questionable; +, weak; ++, strong; +++, very strong; IR, irritant reaction.

agent nor composition of the SL influences skin penetration of SL, but the type of formulation and SL content do (3,4). Skin penetration of *Arnica* SL from a tincture proved to be higher than from a gel preparation, and pure SL in an alcoholic solution had the lowest penetration rate (5). In the present test series *Arnica* SL of the helenalin and dihydrohelenalin type did not play a major role in positive tests to *Arnica*. The test concentration of 0.025% for pure *Arnica* SL was chosen to be comparable to that of alantolactone, costunolide, and dehydrocostunolide each contained with 0.03% in the 0.1% SL mix. With this, the concentration was twice as high as the SL content of the commercial *Arnica* products tested (SL 0.013%) and high enough to elicit positive skin reactions in sensitized patients, as demonstrated by the two patients who reacted to 0.025% dihydrohelenalin-methacrylate. The positive reactions to *Arnica montana* cv. Arbo and eastern European *Arnica*, which both contain relevant amounts of helenalinderivatives, may be due to these SL. While other SL of *Arnica* species such as xanthalongin are present in *Arnica longifolia* (6), monoterpene esters have also to be considered as possible sensitizers in *Arnica montana* (7). Several recent studies revealed that SL mix detects Compositae allergies with lower reliability than Compositae mix (8–10). Patients previously reactive to *Arnica* standard test also responded to a variety of commercial *Arnica*-containing preparations, but only one out of three tested positive for SL mix (11). Similarly, in the present study, the sensitization to *Arnica* was not correlated to the SL contained in the *Arnica* extracts. The commercially available *Arnica* patch test only detected five out of eight existing *Arnica* allergies. It would be desirable to standardize the content of allergenic components in the *Arnica* extract or to test with individual components. Previous studies using the guinea-pig sensitization test have resulted in the classification of *Arnica* as a plant with a strong contact sensitizing potency (12). In contrast, in the well-established mouse model of contact hypersensitivity it has been demonstrated that *Arnica* extracts or purified *Arnica* SLs are unable to induce delayed hypersensitivity in mice with an intact immune system (2).

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