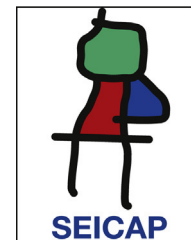




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REVIEW

Rosmarinus officinalis L. as cause of contact dermatitis

M. Miroddi^a, G. Calapai^{a,b,*}, S. Isola^{a,c}, P.L. Minciullo^{a,c}, S. Gangemi^{a,c,d}

^a Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy

^b Operative Unit of Clinical Pharmacology, Azienda Ospedaliera Universitaria Policlinico "G. Martino", Messina, Italy

^c Operative Unit of Allergy and Clinical Immunology, Azienda Ospedaliera Universitaria Policlinico "G. Martino", Messina, Italy

^d Institute of Biomedicine and Molecular Immunology "A. Monroy" (IBIM), Consiglio Nazionale Delle Ricerche (CNR), Palermo, Italy

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Abstract Because of the widespread use of botanicals, it has become crucial for health professionals to improve their knowledge about safety problems. Several herbal medicines contain chemicals with allergenic properties responsible for contact dermatitis. Among these, one is *Rosmarinus officinalis* L. (rosemary), a plant used since ancient times in folk medicine; at the present time it is used worldwide as a spice and flavouring agent, as a preservative and for medicinal and cosmetic purposes.

The present article aims to revise and summarise scientific literature reporting cases of contact dermatitis caused by the use of *R. officinalis* as a raw material or as herbal preparations.

Published case reports were researched on the following databases and search engines: PUBMED, MEDLINE, EMBASE, Google Scholar, Scopus. The used keywords were: *R. officinalis* and *rosemary* each alone or combined with the words *allergy*, *contact dermatitis*, *allergic contact dermatitis*, *sensitisation* and *occupational dermatitis*.

The published case reports show that both rosemary extracts and raw material can be responsible for allergic contact dermatitis. Two cases related to contact dermatitis caused by cross-reactivity between rosemary and thyme were also commented. The diterpene carnosol, a chemical constituent of this plant, has been imputed as a common cause for this reaction.

The incidence of contact dermatitis caused by rosemary is not common, but it could be more frequent with respect to the supposed occurrence. It seems plausible that cases of contact dermatitis caused by rosemary are more frequent with respect to the supposed occurrence, because they could be misdiagnosed. For this reason, this possibility should be carefully considered in dermatitis differential diagnosis.

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* Corresponding author.

E-mail address: gcalapai@unime.it (G. Calapai).

Introduction

During recent years the use of herbal medicine has increased in the western world and, at the same time, the scientific community has shown a raising interest in this field of research. Many herbal medicines commonly used in phytotherapy contain allergenic compounds able to elicit hypersensitivity reactions such as contact dermatitis. In the light of the widespread use of herbal medicines it is crucial for physicians, pharmacists, nurses and all other health professionals to know and to understand more deeply this health issue. Contact dermatitis due to plants is common and several plant families are involved.¹ Among these plants, a herbal medicine used worldwide, *Rosmarinus officinalis* L., can potentially cause this kind of dermal problem.

Methods

Two investigators independently examined the following databases and search engines until December 2012, PUBMED, MEDLINE, EMBASE, Google Scholar, Scopus. No restrictions about language, document format and date have been used in the search strategy to minimise possible bias. The research was operated using the keywords *R. officinalis* and *rosemary* alone or combined with the words *allergy*, *contact dermatitis*, *allergic contact dermatitis*, *sensitisation* and *occupational dermatitis*. We included case reports of contact dermatitis caused by use of *R. officinalis* as a raw material or its herbal preparations.

R. officinalis L.

R. officinalis L. (rosemary is the common English name) belongs to the Labiatae family (Lamiaceae); it is a plant native of the Mediterranean area, with a millennial history of use. It has been used for thousands of years, since ancient Greece and Rome as a medicinal and aromatic herb.² At the present time its use is spread worldwide.

The leaves are sessile, tough, linear to linear-lanceolate, 10–40 mm long and 2–4 mm wide, and have round edges. The upper surface is dark green and glabrous, the lower surface is greyish-green and densely tomentose with a prominent midrib.^{3,4} It is commonly utilised as a spice and flavouring agent, and also as a preservative. Furthermore, the plant possesses properties useful for medicinal and cosmetic purposes. Its essential oil is therapeutically used, in particular in balneology. In folk medicine it is used as antispasmodic in renal colic and dysmenorrhoea, in relieving respiratory disorders and to stimulate growth of hair.⁵

For medicinal purpose, dried leaves and essential oil are used. Preparations based on essential oil or obtained from dried leaves were both recognised useful for the following traditional medicinal uses: by oral use for symptomatic relief of dyspepsia and mild spasmodic disorders of the gastrointestinal tract; by cutaneous use or as a bath additive as an adjuvant in the relief of minor muscular and articular pain and in minor peripheral circulatory disorders.⁴ This was due to the antispasmodic properties of rosemary which relaxes trachea and intestinal smooth muscles, as well as to its choleric activity.⁵ Rosemary, in particular its phenolic constituents, has also been found to exert protective effects

on colonic cancer and other types of cancer through several mechanisms.⁶

Chemical composition

Many studies investigated the chemical composition of *R. officinalis* plant parts employed for medicinal aims. Leaves contain 1,2-cineole, α -pinene, apigenin, betulin, betulinic acid, caffeic acid, camphor, carnosic acid, carnosol, carnosol isomer, methyl myrcene carnosate, cirsimaritin, diosmin, hesperidin, limonene, luteolin 3'-O-beta-D-glucuronide, luteolin 3'-O-(3''-O-acetyl)-beta-D-glucuronide, oleanolic acid, rosmadial, rosmanol, rosmarinic acid, scutellarein, thymol, ursolic acid.^{7,8} A diterpene, rosmariquinone, has been isolated from a methanolic extract of *R. officinalis* L.⁹

Essential oil contains monoterpenes, phenols, sesquiterpenes, monoterpenoid ethers, monoterpenoid ketones, monoterpenoid alcohols, and monoterpenoid esters, camphor, eucalyptol, α -pinene, borneol.¹⁰ The main components with antioxidant properties are phenolic diterpenes as carnosol and carnosic acid.^{11,12}

The main active compounds of rosemary include caffeic acid, rosmarinic acid (RA), ursolic acid (UA), carnosic acid (CA), and carnosol.^{13,14} Carnosol is a natural phytopolyphenol with antimicrobial, antioxidant and anticarcinogen functions.⁶ For its antimicrobial and antioxidant activities rosemary has been utilised in the food-processing industry.¹⁵

Contact dermatitis

Contact dermatitis (CD) is an inflammatory skin condition caused by the exposure to exogenous agents. Two main types of contact dermatitis may be distinguished: irritant contact dermatitis (ICD), due to pro-inflammatory and toxic factors able to activate the skin innate immunity; and allergic contact dermatitis (ACD), which is a T-cell-mediated hypersensitivity reaction.^{16,17} It is characterised by itching with erythema, vesicles and bullae in acute phase and by lichen with cracks and fissures in chronic phase.¹⁷ CD is a highly frequent disease with a significant influence on the quality of life of the affected patients and a relevant socioeconomic impact.¹⁸ The occurrence of allergic contact dermatitis increases with age; prevalence rates of 15–20% have been reported in the Western world; however, many cases may pass unnoticed, so it is not simple to establish the frequency of this affection. Today the compounds (hap- tens) able to cause the disease are more than 4350. Age and gender do not represent risk factors, whereas the occupational activity is the main condition implicated in the onset of allergic contact dermatitis.¹⁹

Overview of case reports regarding contact dermatitis caused by *R. officinalis*

R. officinalis was indicated as a cause of contact dermatitis by Klarman in 1958 and by Flosserau and Benezra in 1970.²⁰ To date, eight cases of contact dermatitis caused by rosemary (or its constituents) and one case of contact dermatitis characterised by cross reaction to *Thymus vulgaris* L. (English common name is thyme) have been published. One of the most important constituents of rosemary is carnosol

(a naturally occurring diterpene), and it has been reported as the cause of allergic contact dermatitis too.¹⁵

A case of occupational contact dermatitis in a 56-year-old man due to the allergenic constituent carnosol contained in a dry extract obtained from leaves of rosemary has been published. The patient, healthy and with no previous history of atopy, had been working for several years in a food (sausages) processing factory where his task was to add spices and additives. A few weeks after the introduction as preservative of a rosemary leaf extract in the production procedure, he developed severe dermatitis on his hands, forearms and face. A clinical recovery occurred during the days off from work and the lesions reoccurred every time he handled the rosemary extract. 30 months after the clinical recovery he presented flares of dermatitis after contact with the rosemary extract. Patch tests were performed to assess the reaction to the extract of rosemary (5% and 10% in pet) and to carnosol (1% and 0.1% dilution in ethanol), the patient showed positivity to rosemary extract (+ at day 2 and 5 both with 5% and 10% extracts) and only to carnosol 1% (+ at day 3 and 7). Furthermore, when carnosol was patch tested in more than 100 controls at 1% and 0.1% dilution, nobody experienced a positive reaction.¹⁵

Another report is about a 56-year-old man. The man applied a rosemary leaf plaster on his knee to treat pain. Three days later, he developed acute itchy vesicular exudative dermatitis in the area of application that improved after withdrawing the plaster. Patch test for rosemary leaf showed positivity on the patient (++) on day 2; +++ on day 4) and resulted negative on 10 controls. Other plants belonging to the Labiatae family (thyme, origanum, mint) were tested with negative results.²¹

Contact dermatitis caused by *rosmarinus* can be aggravated by sun exposure. A 62-year-old non-atopic woman after handling fresh rosemary on sunny days presented several episodes characterised by itchy dermatitis lesions over exposed areas (hand, forearm and face). The lesions appeared hours after handling rosemary leaves and improved within seven days of treatment with topical corticosteroids. Prick-by-prick testing with rosemary leaves was carried out with negative results at 15 min. Patch test showed a positive reaction (++) at day 2 to rosemary leaves and also to mint, oregano, and thyme. Photopatch tests with rosemary and thyme showed stronger reactions. Tests performed on five control subjects were negative.²²

Habitual gastronomic use of rosemary as in food has been associated with the development of chronic contact cheilitis.²³ A 48-year-old woman with medical history including allergic rhinitis and asthmatic bronchitis developed oedema and eczematous lesions on her hands, eyelids and face a few hours after taking a walk where she touched several plants. Patch and photopatch with perfume series were negative. Patch and photopatch testing to rosemary extract at 1% were positive (+++), and so was the patch to rosemary leaf (more intense with photopatch ++/+++ and to hydrophilic and lipophilic rosemary extracts 10% (+++). Patch test to carnosol at 0.1% concentration was also positive (++)²⁴

Another case of allergic contact dermatitis due to an extract of rosemary was reported in a 23-year-old woman, with a past history of atopic dermatitis. The woman presented itchy scaly erythema and red papules around her

eyes and nose and on her cheeks for about a month after using various cosmetics and a cleansing gel containing rosemary leaf extract. The cleansing gel had been used for two months. Patch test was positive on day 3 to the cleansing gel (1% in distilled water) (+) and to the rosemary leaf extract (0.1% in distilled water) (+). Two weeks after ceasing the use of the cleansing gel and rosemary extract, the eruption disappeared.²⁵

Two cases of contact dermatitis caused by both rosemary and thymus have been reported.

A 45-year-old man developed an acute cutaneous eczematous, severely itching lesion a few hours after a 24-hr application of a herbs poultice to treat muscular pain, on his right thigh. The herbs poultice contained a mix of *R. officinalis*, *T. vulgaris* (thyme), *Arnica montana* (arnica), *Anthemis arvensis* (chamomile), and *Equisetum arvense* (horsetails). The cutaneous lesion had a tendency to form vesicles and blisters and required hospitalisation. No previous contact with other plants of the Labiatae family was reported by the patient. He was then treated with topical and oral corticosteroids for two weeks and the lesion healed completely. Patch testing for the poultice 'as it is' was positive (+ on day 2 and 4), to rosemary (++) on day 2 and 4) and to thyme (– on day 2; ++ on day 4) and it was negative to arnica, chamomile, and horsetails. Healthy control studies were performed with rosemary and thyme 'as it is' in 12 subjects, with negative results.²⁰

A 53-year-old man developed several episodes of skin reactions characterised by an itching and erythematous eruption and severe swelling of his face, chest and dorsal aspect of arms for two years. The man used to apply a homemade alcoholic preparation on his thorax, containing a mixture of several plants belonging to the Labiatae family, as a balsam. Epicutaneous tests were done with the commercial plant series and in addition with flowers and leaves from the following plants: rosemary, sage, oregano, thyme and lavender. Results were positive for rosemary: dried leaves with water, +++ on day 1, +++ on day 2, +++ on day 3; dried leaves, + on day 1, + on day 2, + on day 3; flowers + on day 1, + on day 2, + on day 3; rosemary alcohol extract (as it is) + on day 1 + on day 2 + on day 3. Results for sage: fresh leaves from the top side ++ on day 1 ++ on day 2 ++ on day 3; fresh leaves from the underside +++ on day 1 +++ on day 2 +++ on day 3. Lavender results: fresh leaves from the top side + on day 1 + on day 2 + on day 3; fresh leaves from the underside – on day 1 + on day 2 + on day 3; fresh leaves from the underside +++ on day 1 +++ on day 2 +++ on day 3. Thyme results: dried leaves – on day 1 + on day 2 + on day 3; dried leaves + water – on day 1 – on day 2 + on day 3. Oregano dried leaves + water – on day 1 – on day 2; uncertain on day 3.²⁶

Conclusions

It is well known that rosemary essential oil, contained in various cosmetic preparations, when topically applied, can cause irritation and photosensitivity.²² The case series above discussed show that both rosemary extracts and raw material can be responsible for allergic contact dermatitis. Furthermore rosemary can determine cross reaction with thyme. The cause of this dermatitis has been imputed the diterpene carnosol, one of the most important constituents

of rosemary. It has been hypothesised that carnosol, as well as its derivative carnosic acid, possesses antioxidant activity, because its concentration is correlated with the free radical scavenging activity shown for rosemary.³ The incidence of contact dermatitis caused by rosemary is not common, but at the same time it seems to be more frequent with respect to the supposed occurrence. *R. officinalis*, as above described, is widely used as food, cosmetic, spice, flavouring and a medicinal ingredient. Allergic contact dermatitis may be more frequently encountered but it could be misdiagnosed. For this reason it should be carefully considered in dermatitis differential diagnosis. Since herbal medicines use has increased greatly, it has become crucial for health professionals to improve their knowledge about safety issues related to these medicines.²⁷

Ethical responsibilities

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this investigation.

Confidentiality of data. The authors declare that no patient data appears in this article.

Right to privacy and informed consent. The authors declare that no patient data appears in this article.

Conflict of interest

None of the co-authors have to declare any conflict of interest.

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